

Anhang 4-G

**Dossier zur Nutzenbewertung
gemäß § 35a SGB V**

*Beclometason/Formoterol/Glycopyrronium
(Trimbow[®])*

Chiesi GmbH

Modul 4A Anhang 4-G

Subgruppenanalysen

Stand: 08.02.2021

Inhaltsverzeichnis

Seite des pdf-Dokuments¹

Subgruppenanalysen zu Endpunktkategorien:

Morbidität: Asthmaexazerbationen	3
Morbidität: Asthmasymptome und -kontrolle.....	273
Morbidität: Notfallmedikation	956
Morbidität: Krankenhausaufenthalte (<i>Health Economics</i>) ²	1128
Morbidität: EQ-5D-3L VAS	1373
Gesundheitsbezogene Lebensqualität: Asthmakontrollfragebogen ACQ-5	1590
Sicherheit: Endpunkte zu unerwünschten Ereignissen.....	1751

¹Dieses Dokument ist über die Lesezeichen-Funktion des pdf-Readers navigierbar.

²Die Analysen zu den Subgruppen „*Body-Mass-Index*“ und „Grad der Reversibilität beim Screening“ konnten für den Endpunkt „Anzahl der Krankenhausaufenthalte wegen Asthma“ wegen der geringen Ereigniszahlen mit dem gewählten statistischen Modell nicht berechnet werden.

ADDITIONAL_TLF_BATCH2_SEVERE_EXACERBATION

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch2

Date of Production: 17/12/2020

Identification Code: Additional_TLF_batch2_Severe_Exacerbation_CCD-05993AB2-02_20201217(Batch2)

Table 19.2.11a Statistical Analysis of Severe Asthma Exacerbations including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.313
Country			0.004**
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Age Group			0.925
Age Group Treatment Interaction			0.834

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.11b Statistical Analysis of Severe Asthma Exacerbations including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.223
Country			0.003**
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Gender			0.304
Gender Treatment Interaction			0.846

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.11c Statistical Analysis of Severe Asthma Exacerbations
including Bmi - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.366
Country			0.004**
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Bmi			0.247
Bmi Treatment Interaction			0.338

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.11d Statistical Analysis of Severe Asthma Exacerbations including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.726
Country			0.007**
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Smoking Status			0.004**
Smoking Status Treatment Interaction			0.015*

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.11e Statistical Analysis of Severe Asthma Exacerbations including Number of exacerbations in the previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.294
Country			0.003**
Number of exacerbations in the previous year			<0.001***
Number of exacerbations in the previous year Treatment Interaction			0.783

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 19.2.11f Statistical Analysis of Severe Asthma Exacerbations including Degree of reversibility at screening - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.261
Country			0.003**
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Degree of reversibility at screening			0.115
Degree of reversibility at screening Treatment Interaction			0.806

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.11g Statistical Analysis of Severe Asthma Exacerbations including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.231
Country			0.004**
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Use of spacer			0.825
Use of spacer Treatment Interaction			0.791

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.11h Statistical Analysis of Severe Asthma Exacerbations including Relevant concomitant cardiovascular disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.257
Country			0.003**
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Relevant concomitant cardiovascular disease			0.058
Relevant concomitant cardiovascular disease Treatment Interaction			0.775

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.11i Statistical Analysis of Severe Asthma Exacerbations including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.249
Number of Asthma Exacerbations in Previous Year (1, >1)			<0.001***
Region			0.493
Region Treatment Interaction			0.782

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.14a Time to First Severe Asthma Exacerbations including Age Group -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.340
Country			<0.001***
Number of Asthma Exacerbations in Previous Year			<0.001***
Age Group			0.837
Age Group Treatment Interaction			0.696

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14b Time to First Severe Asthma Exacerbations including Gender -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.126
Country			<0.001***
Number of Asthma Exacerbations in Previous Year			<0.001***
Gender			0.178
Gender Treatment Interaction			0.382

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14c Time to First Severe Asthma Exacerbations including Bmi -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.272
Country			0.001**
Number of Asthma Exacerbations in Previous Year			<0.001***
Bmi			0.717
Bmi Treatment Interaction			0.869

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14d Time to First Severe Asthma Exacerbations including Smoking Status -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.038*
Country			0.002**
Number of Asthma Exacerbations in Previous Year			<0.001***
Smoking Status			0.013*
Smoking Status Treatment Interaction			0.071

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14e Time to First Severe Asthma Exacerbations including Number of exacerbations in the previous year -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.483
Country			<0.001***
Number of exacerbations in the previous year			0.005**
Number of exacerbations in the previous year Treatment Interaction			0.788

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment and country as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14f Time to First Severe Asthma Exacerbations including Degree of reversibility at screening -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	451	240	
Effect			
Treatment			0.219
Country			<0.001***
Number of Asthma Exacerbations in Previous Year			<0.001***
Degree of reversibility at screening			0.123
Degree of reversibility at screening Treatment Interaction			0.720

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14g Time to First Severe Asthma Exacerbations including Use of spacer -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.244
Country			<0.001***
Number of Asthma Exacerbations in Previous Year			<0.001***
Use of spacer			0.956
Use of spacer Treatment Interaction			0.662

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14h Time to First Severe Asthma Exacerbations including Relevant concomitant cardiovascular disease -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.321
Country			<0.001***
Number of Asthma Exacerbations in Previous Year			<0.001***
Relevant concomitant cardiovascular disease			0.206
Relevant concomitant cardiovascular disease Treatment Interaction			0.866

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.14i Time to First Severe Asthma Exacerbations including Region -
Cox Proportional Hazards Analysis Interaction Test
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	452	240	
Effect			
Treatment			0.399
Number of Asthma Exacerbations in Previous Year			<0.001***
Region			0.431
Region Treatment Interaction			0.951

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment and number of asthma exacerbations as factors
[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12a Statistical Analysis of Severe Asthma Exacerbations stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.078	
Country				0.002**	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.264 [0.213, 0.326]	0.324 [0.264, 0.397]	0.215 [0.157, 0.295]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.814 [0.610, 1.086] 0.161
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.224 [0.842, 1.779] 0.290
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.665 [0.460, 0.962] 0.030*

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12a Statistical Analysis of Severe Asthma Exacerbations stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.383	
Country				0.082	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.022*	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.276 [0.177, 0.429]	0.340 [0.233, 0.497]	0.193 [0.090, 0.413]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.811 [0.462, 1.423] 0.465
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.429 [0.606, 3.369] 0.414
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.567 [0.248, 1.301] 0.181

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Age Group: <65 years old CHF 5993 pMDI HS (N=571)					
[0-4)	473	11	2, (0.004)	0.023	0.013, 0.042
[4-12)	460	38	7, (0.012)	0.081	0.060, 0.110
[12-26)	429	65	13, (0.023)	0.139	0.111, 0.174
[26-40)	396	87	22, (0.039)	0.188	0.155, 0.226
[40-52)	367	98	180, (0.315)	0.212	0.177, 0.252
[52-EoT]	233	98	452, (0.792)	0.212	0.177, 0.252
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	49.14, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Applicable

- Notes: [1] * Severe Asthma Exacerbations
 [2] EoT = End of Treatment
 [3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	448	14	4, (0.007)	0.031	0.019, 0.052
[4-12)	431	36	9, (0.016)	0.081	0.059, 0.111
[12-26)	405	66	17, (0.030)	0.150	0.120, 0.186
[26-40)	370	88	25, (0.044)	0.200	0.166, 0.241
[40-52)	344	104	174, (0.305)	0.238	0.201, 0.281
[52-EoT]	213	106	433, (0.758)	0.238	0.201, 0.281
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	53.00	41.14, NonEst			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	246	7	3, (0.010)	0.029	0.014, 0.059
[4-12)	236	12	5, (0.017)	0.049	0.028, 0.085
[12-26)	230	21	13, (0.045)	0.087	0.058, 0.130
[26-40)	214	32	18, (0.063)	0.134	0.097, 0.185
[40-52)	200	40	93, (0.324)	0.169	0.127, 0.224
[52-EoT]	125	40	240, (0.836)	0.169	0.127, 0.224
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Age Group: >= 65 years old CHF 5993 pMDI HS (N=571)					
[0-4)	98	4	2, (0.004)	0.041	0.016, 0.105
[4-12)	94	7	7, (0.012)	0.072	0.035, 0.145
[12-26)	90	14	13, (0.023)	0.144	0.088, 0.231
[26-40)	83	18	22, (0.039)	0.186	0.121, 0.278
[40-52)	77	21	180, (0.315)	0.217	0.148, 0.314
[52-EoT]	39	21	452, (0.792)	0.217	0.148, 0.314
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	36.29, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	123	6	4, (0.007)	0.049	0.022, 0.106
[4-12)	116	13	9, (0.016)	0.107	0.063, 0.177
[12-26)	108	25	17, (0.030)	0.208	0.146, 0.292
[26-40)	93	31	25, (0.044)	0.260	0.190, 0.349
[40-52)	83	32	174, (0.305)	0.269	0.198, 0.358
[52-EoT]	48	32	433, (0.758)	0.269	0.198, 0.358
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	34.86	20.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	41	0	3, (0.010)	0.000	NonEst, NonEst
[4-12)	41	3	5, (0.017)	0.074	0.025, 0.213
[12-26)	37	3	13, (0.045)	0.074	0.025, 0.213
[26-40)	36	6	18, (0.063)	0.156	0.073, 0.316
[40-52)	31	6	93, (0.324)	0.156	0.073, 0.316
[52-EoT]	23	7	240, (0.836)	0.156	0.073, 0.316
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	52.71	35.57, NonEst			
50th Percentile	NonEst	52.71, NonEst			
75th Percentile	NonEst	52.71, NonEst			

Produced: 17 December 2020 Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13a Time to First Severe Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15a Time to First Severe Asthma Exacerbations by Age Group - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Age Group: <65 years old						
Number of Patients Included in Model	473	448	246			
Number of Censored Patients	375	342	206			
Treatment				0.097		
Country				0.007**		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.862 [0.654, 1.135]	0.289
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.282 [0.886, 1.853]	0.187
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.672 [0.467, 0.968]	0.033*

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15a Time to First Severe Asthma Exacerbations by Age Group - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Age Group: >= 65 years old						
Number of Patients Included in Model	98	123	41			
Number of Censored Patients	77	91	34			
Effect						
Treatment				0.314		
Country				0.086		
Number of Asthma Exacerbations in Previous Year				0.020*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.791 [0.449, 1.393]	0.417
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.474 [0.609, 3.567]	0.389
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.536 [0.232, 1.242]	0.146

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors
 [2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12b Statistical Analysis of Severe Asthma Exacerbations stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.047*	
Country				0.152	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.227 [0.160, 0.323]	0.340 [0.254, 0.454]	0.173 [0.101, 0.296]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.668 [0.427, 1.046] 0.078
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.315 [0.697, 2.481] 0.398
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.508 [0.277, 0.932] 0.029*

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12b Statistical Analysis of Severe Asthma Exacerbations stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.276	
Country				0.002**	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.286 [0.227, 0.359]	0.327 [0.260, 0.412]	0.237 [0.168, 0.333]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.872 [0.637, 1.194] 0.393
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.208 [0.807, 1.808] 0.359
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.722 [0.483, 1.081] 0.113

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Gender: Male					
CHF 5993 pMDI HS (N=571)					
[0-4)	212	9	2, (0.004)	0.042	0.022, 0.080
[4-12)	203	15	7, (0.012)	0.071	0.043, 0.115
[12-26)	195	32	13, (0.023)	0.152	0.110, 0.208
[26-40)	176	38	22, (0.039)	0.181	0.135, 0.240
[40-52)	167	39	180, (0.315)	0.186	0.140, 0.246
[52-EoT]	105	39	452, (0.792)	0.186	0.140, 0.246
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	244	7	4, (0.007)	0.029	0.014, 0.059
[4-12)	235	22	9, (0.016)	0.091	0.061, 0.135
[12-26)	218	43	17, (0.030)	0.180	0.137, 0.235
[26-40)	192	54	25, (0.044)	0.227	0.179, 0.286
[40-52)	179	58	174, (0.305)	0.245	0.195, 0.305
[52-EoT]	111	58	433, (0.758)	0.245	0.195, 0.305
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	28.43, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	103	2	3, (0.010)	0.019	0.005, 0.075
[4-12)	100	5	5, (0.017)	0.049	0.021, 0.114
[12-26)	96	7	13, (0.045)	0.069	0.033, 0.139
[26-40)	92	9	18, (0.063)	0.090	0.048, 0.165
[40-52)	88	11	93, (0.324)	0.111	0.063, 0.191
[52-EoT]	56	12	240, (0.836)	0.111	0.063, 0.191
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	52.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Gender: Female					
CHF 5993 pMDI HS (N=571)					
[0-4)	359	6	2, (0.004)	0.017	0.008, 0.037
[4-12)	351	30	7, (0.012)	0.084	0.060, 0.119
[12-26)	324	47	13, (0.023)	0.133	0.102, 0.173
[26-40)	303	67	22, (0.039)	0.191	0.153, 0.236
[40-52)	277	80	180, (0.315)	0.229	0.188, 0.277
[52-EoT]	167	80	452, (0.792)	0.229	0.188, 0.277
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	44.00, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	327	13	4, (0.007)	0.040	0.023, 0.068
[4-12)	312	27	9, (0.016)	0.083	0.058, 0.119
[12-26)	295	48	17, (0.030)	0.149	0.114, 0.192
[26-40)	271	65	25, (0.044)	0.203	0.162, 0.251
[40-52)	248	78	174, (0.305)	0.245	0.201, 0.296
[52-EoT]	150	80	433, (0.758)	0.245	0.201, 0.296
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	53.00	38.14, NonEst			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	184	5	3, (0.010)	0.027	0.011, 0.064
[4-12)	177	10	5, (0.017)	0.055	0.030, 0.100
[12-26)	171	17	13, (0.045)	0.094	0.060, 0.147
[26-40)	158	29	18, (0.063)	0.164	0.117, 0.227
[40-52)	143	35	93, (0.324)	0.199	0.147, 0.266
[52-EoT]	92	35	240, (0.836)	0.199	0.147, 0.266
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	48.43, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13b Time to First Severe Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15b Time to First Severe Asthma Exacerbations by Gender - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Gender: Male						
Number of Patients Included in Model	212	244	103			
Number of Censored Patients	173	186	91			
Treatment				0.043*		
Country				0.232		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.767 [0.509, 1.156]	0.205
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.657 [0.864, 3.180]	0.129
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.463 [0.248, 0.864]	0.016*

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15b Time to First Severe Asthma Exacerbations by Gender - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Gender: Female						
Number of Patients Included in Model	359	327	184			
Number of Censored Patients	279	247	149			
Effect						
Treatment				0.372		
Country				0.004**		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.889 [0.651, 1.213]	0.457
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.178 [0.791, 1.754]	0.420
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.754 [0.507, 1.123]	0.165

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12c Statistical Analysis of Severe Asthma Exacerbations stratified by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.119	
Country				0.050	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.371	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.190 [0.123, 0.295]	0.335 [0.237, 0.474]	0.225 [0.126, 0.402]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.569 [0.326, 0.990] 0.046*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.846 [0.413, 1.731] 0.646
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.672 [0.343, 1.318] 0.248

Produced: 17 December 2020

Page 1 of 3

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12c Statistical Analysis of Severe Asthma Exacerbations stratified by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30)					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.247	
Country				0.030*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.002**	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.248 [0.182, 0.337]	0.269 [0.196, 0.369]	0.163 [0.098, 0.272]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.921 [0.598, 1.418] 0.708
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.517 [0.847, 2.719] 0.161
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.607 [0.335, 1.099] 0.099

Produced: 17 December 2020

Page 2 of 3

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12c Statistical Analysis of Severe Asthma Exacerbations stratified by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.099	
Country				0.013*	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.310 [0.232, 0.413]	0.392 [0.300, 0.512]	0.229 [0.147, 0.357]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.789 [0.540, 1.155] 0.224
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.350 [0.806, 2.262] 0.254
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.585 [0.353, 0.968] 0.037*

Produced: 17 December 2020

Page 3 of 3

Source: Listing Not Applicable

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
BMI Class: < 25					
CHF 5993 pMDI HS (N=571)					
[0-4)	150	3	2, (0.004)	0.020	0.006, 0.061
[4-12)	147	8	7, (0.012)	0.054	0.027, 0.104
[12-26)	140	17	13, (0.023)	0.115	0.073, 0.179
[26-40)	128	22	22, (0.039)	0.150	0.102, 0.219
[40-52)	121	25	180, (0.315)	0.172	0.119, 0.243
[52-EoT]	81	25	452, (0.792)	0.172	0.119, 0.243
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 1 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	163	7	4, (0.007)	0.043	0.021, 0.088
[4-12)	156	17	9, (0.016)	0.104	0.066, 0.162
[12-26)	146	26	17, (0.030)	0.160	0.112, 0.226
[26-40)	135	34	25, (0.044)	0.210	0.155, 0.282
[40-52)	124	37	174, (0.305)	0.230	0.172, 0.303
[52-EoT]	79	38	433, (0.758)	0.230	0.172, 0.303
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	53.00	32.14, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	73	2	3, (0.010)	0.027	0.007, 0.105
[4-12)	71	5	5, (0.017)	0.068	0.029, 0.157
[12-26)	68	5	13, (0.045)	0.068	0.029, 0.157
[26-40)	64	7	18, (0.063)	0.099	0.048, 0.196
[40-52)	59	11	93, (0.324)	0.162	0.093, 0.274
[52-EoT]	36	11	240, (0.836)	0.162	0.093, 0.274
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	49.00, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 3 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
BMI Class: [25-30) CHF 5993 pMDI HS (N=571)					
[0-4)	217	3	2, (0.004)	0.014	0.004, 0.042
[4-12)	212	12	7, (0.012)	0.056	0.032, 0.096
[12-26)	202	27	13, (0.023)	0.126	0.088, 0.178
[26-40)	186	36	22, (0.039)	0.168	0.124, 0.226
[40-52)	174	44	180, (0.315)	0.207	0.158, 0.268
[52-EoT]	96	44	452, (0.792)	0.207	0.158, 0.268
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	47.14, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 5 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	205	5	4, (0.007)	0.025	0.010, 0.058
[4-12)	198	12	9, (0.016)	0.059	0.034, 0.102
[12-26)	187	26	17, (0.030)	0.131	0.091, 0.186
[26-40)	169	32	25, (0.044)	0.162	0.117, 0.221
[40-52)	160	40	174, (0.305)	0.204	0.154, 0.268
[52-EoT]	95	40	433, (0.758)	0.204	0.154, 0.268
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	47.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	112	4	3, (0.010)	0.036	0.014, 0.093
[4-12)	105	6	5, (0.017)	0.055	0.025, 0.117
[12-26)	101	9	13, (0.045)	0.083	0.044, 0.153
[26-40)	96	15	18, (0.063)	0.141	0.087, 0.223
[40-52)	88	16	93, (0.324)	0.151	0.095, 0.234
[52-EoT]	56	17	240, (0.836)	0.151	0.095, 0.234
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	52.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 7 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
BMI Class: >=30					
CHF 5993 pMDI HS (N=571)					
[0-4)	204	9	2, (0.004)	0.044	0.023, 0.083
[4-12)	195	25	7, (0.012)	0.123	0.085, 0.177
[12-26)	177	35	13, (0.023)	0.173	0.128, 0.233
[26-40)	165	47	22, (0.039)	0.234	0.182, 0.299
[40-52)	149	50	180, (0.315)	0.250	0.195, 0.316
[52-EoT]	95	50	452, (0.792)	0.250	0.195, 0.316
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	29.86, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 9 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	203	8	4, (0.007)	0.040	0.020, 0.077
[4-12)	193	20	9, (0.016)	0.100	0.065, 0.150
[12-26)	180	39	17, (0.030)	0.195	0.147, 0.257
[26-40)	159	53	25, (0.044)	0.266	0.211, 0.334
[40-52)	143	59	174, (0.305)	0.297	0.239, 0.366
[52-EoT]	87	60	433, (0.758)	0.297	0.239, 0.366
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	34.00	25.71, NonEst			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	53.57, NonEst			

Produced: 17 December 2020 Page 10 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	102	1	3, (0.010)	0.010	0.001, 0.068
[4-12)	101	4	5, (0.017)	0.039	0.015, 0.101
[12-26)	98	10	13, (0.045)	0.099	0.054, 0.176
[26-40)	90	16	18, (0.063)	0.159	0.100, 0.246
[40-52)	84	19	93, (0.324)	0.189	0.125, 0.280
[52-EoT]	56	19	240, (0.836)	0.189	0.125, 0.280
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	42.43, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 11 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13c Time to First Severe Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 12 of 12

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15c Time to First Severe Asthma Exacerbations by Bmi - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
BMI Class: < 25						
Number of Patients Included in Model	150	163	73			
Number of Censored Patients	125	125	62			
Treatment				0.285		
Country				0.096		
Number of Asthma Exacerbations in Previous Year				0.068		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.723 [0.435, 1.202]	0.211
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.139 [0.556, 2.335]	0.722
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.635 [0.321, 1.257]	0.192

Produced: 17 December 2020 Page 1 of 3

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15c Time to First Severe Asthma Exacerbations by Bmi - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
BMI Class: [25-30)						
Number of Patients Included in Model	217	205	112			
Number of Censored Patients	173	165	95			
Treatment				0.497		
Country				0.069		
Number of Asthma Exacerbations in Previous Year				0.043*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.946 [0.613, 1.459]	0.801
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.332 [0.757, 2.344]	0.320
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.710 [0.397, 1.268]	0.247

Produced: 17 December 2020 Page 2 of 3

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15c Time to First Severe Asthma Exacerbations by Bmi - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
BMI Class: >=30						
Number of Patients Included in Model	204	203	102			
Number of Censored Patients	154	143	83			
Effect						
Treatment				0.132		
Country				0.032*		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.808 [0.554, 1.179]	0.270
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.357 [0.798, 2.308]	0.260
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.596 [0.355, 1.001]	0.051

Produced: 17 December 2020 Page 3 of 3

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12d Statistical Analysis of Severe Asthma Exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.002**	
Country				0.004**	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.261 [0.212, 0.321]	0.327 [0.270, 0.396]	0.164 [0.117, 0.231]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.797 [0.605, 1.051] 0.108
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.588 [1.073, 2.349] 0.021*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.502 [0.341, 0.739] 0.000***

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12d Statistical Analysis of Severe Asthma Exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.256	
Country				0.134	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.205	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.276 [0.167, 0.455]	0.400 [0.254, 0.630]	0.518 [0.285, 0.942]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.689 [0.355, 1.341] 0.273
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.532 [0.246, 1.151] 0.109
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.296 [0.613, 2.742] 0.497

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Smoking Status: Non smoker CHF 5993 pMDI HS (N=571)					
[0-4)	488	11	2, (0.004)	0.023	0.013, 0.040
[4-12)	475	39	7, (0.012)	0.081	0.060, 0.109
[12-26)	443	67	13, (0.023)	0.139	0.111, 0.173
[26-40)	410	88	22, (0.039)	0.184	0.152, 0.221
[40-52)	383	99	180, (0.315)	0.207	0.173, 0.246
[52-EoT]	235	99	452, (0.792)	0.207	0.173, 0.246
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	491	16	4, (0.007)	0.033	0.020, 0.053
[4-12)	471	40	9, (0.016)	0.082	0.061, 0.110
[12-26)	443	73	17, (0.030)	0.151	0.122, 0.187
[26-40)	404	99	25, (0.044)	0.206	0.173, 0.245
[40-52)	372	116	174, (0.305)	0.243	0.207, 0.284
[52-EoT]	229	118	433, (0.758)	0.243	0.207, 0.284
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	53.00	40.86, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	245	5	3, (0.010)	0.020	0.009, 0.048
[4-12)	237	10	5, (0.017)	0.041	0.022, 0.075
[12-26)	230	15	13, (0.045)	0.062	0.038, 0.101
[26-40)	219	27	18, (0.063)	0.114	0.080, 0.162
[40-52)	204	34	93, (0.324)	0.145	0.106, 0.197
[52-EoT]	129	35	240, (0.836)	0.145	0.106, 0.197
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	52.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments					
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Smoking Status: Ex-smoker CHF 5993 pMDI HS (N=571)					
[0-4)	83	4	2, (0.004)	0.048	0.018, 0.123
[4-12)	79	6	7, (0.012)	0.073	0.033, 0.154
[12-26)	76	12	13, (0.023)	0.146	0.086, 0.243
[26-40)	69	17	22, (0.039)	0.210	0.136, 0.316
[40-52)	61	20	180, (0.315)	0.250	0.169, 0.360
[52-EoT]	37	20	452, (0.792)	0.250	0.169, 0.360
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	29.14, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	80	4	4, (0.007)	0.050	0.019, 0.128
[4-12)	76	9	9, (0.016)	0.113	0.061, 0.207
[12-26)	70	18	17, (0.030)	0.228	0.150, 0.337
[26-40)	59	20	25, (0.044)	0.255	0.172, 0.367
[40-52)	55	20	174, (0.305)	0.255	0.172, 0.367
[52-EoT]	32	20	433, (0.758)	0.255	0.172, 0.367
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	38.14	12.86, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	42	2	3, (0.010)	0.048	0.012, 0.177
[4-12)	40	5	5, (0.017)	0.119	0.051, 0.263
[12-26)	37	9	13, (0.045)	0.216	0.119, 0.375
[26-40)	31	11	18, (0.063)	0.270	0.159, 0.436
[40-52)	27	12	93, (0.324)	0.297	0.181, 0.465
[52-EoT]	19	12	240, (0.836)	0.297	0.181, 0.465
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	37.29	8.14, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13d Time to First Severe Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15d Time to First Severe Asthma Exacerbations by Smoking Status - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Smoking Status: Non smoker						
Number of Patients Included in Model	488	491	245			
Number of Censored Patients	389	373	210			
Treatment				0.009**		
Country				0.033*		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.824 [0.630, 1.076]	0.155
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.479 [1.005, 2.176]	0.047*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.557 [0.382, 0.812]	0.002**

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15d Time to First Severe Asthma Exacerbations by Smoking Status - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Smoking Status: Ex-smoker						
Number of Patients Included in Model	83	80	42			
Number of Censored Patients	63	60	30			
Effect						
Treatment				0.760		
Country				0.014*		
Number of Asthma Exacerbations in Previous Year				0.039*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.830 [0.442, 1.558]	0.562
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.781 [0.375, 1.625]	0.509
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.063 [0.507, 2.230]	0.872

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12e Statistical Analysis of Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	451	229		
Effect					
Treatment				0.036*	
Country				0.002**	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.218 [0.171, 0.277]	0.285 [0.229, 0.354]	0.168 [0.117, 0.242]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.766 [0.556, 1.057] 0.105
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.298 [0.842, 2.001] 0.238
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.590 [0.387, 0.900] 0.014*

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 19.2.12e Statistical Analysis of Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.469	
Country				0.003**	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.542 [0.401, 0.732]	0.584 [0.431, 0.791]	0.413 [0.257, 0.665]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.928 [0.606, 1.420] 0.730
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.311 [0.750, 2.293] 0.342
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.708 [0.407, 1.231] 0.221

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Number of Exacerbation in the Previous year: 1					
CHF 5993 pMDI HS (N=571)					
[0-4)	439	7	2, (0.004)	0.016	0.008, 0.033
[4-12)	431	25	7, (0.012)	0.057	0.039, 0.084
[12-26)	409	52	13, (0.023)	0.120	0.093, 0.154
[26-40)	378	67	22, (0.039)	0.155	0.124, 0.193
[40-52)	356	75	180, (0.315)	0.174	0.142, 0.214
[52-EoT]	218	75	452, (0.792)	0.174	0.142, 0.214
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	451	14	4, (0.007)	0.031	0.019, 0.052
[4-12)	433	31	9, (0.016)	0.070	0.049, 0.097
[12-26)	411	59	17, (0.030)	0.133	0.105, 0.169
[26-40)	377	79	25, (0.044)	0.180	0.147, 0.219
[40-52)	351	90	174, (0.305)	0.205	0.171, 0.246
[52-EoT]	215	92	433, (0.758)	0.205	0.171, 0.246
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	53.57	53.00, NonEst			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	229	4	3, (0.010)	0.017	0.007, 0.046
[4-12)	224	9	5, (0.017)	0.040	0.021, 0.075
[12-26)	217	14	13, (0.045)	0.062	0.037, 0.103
[26-40)	204	24	18, (0.063)	0.109	0.074, 0.158
[40-52)	191	29	93, (0.324)	0.132	0.094, 0.185
[52-EoT]	121	30	240, (0.836)	0.132	0.094, 0.185
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	52.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Number of Exacerbation in the Previous year: > 1					
CHF 5993 pMDI HS (N=571)					
[0-4)	132	8	2, (0.004)	0.061	0.031, 0.118
[4-12)	123	20	7, (0.012)	0.153	0.102, 0.227
[12-26)	110	27	13, (0.023)	0.208	0.147, 0.288
[26-40)	101	38	22, (0.039)	0.295	0.224, 0.382
[40-52)	88	44	180, (0.315)	0.343	0.268, 0.432
[52-EoT]	54	44	452, (0.792)	0.343	0.268, 0.432
Percentile	Estimates (Weeks)		95% CI		
25th Percentile	31.14		15.14, 42.00		
50th Percentile	NonEst		NonEst, NonEst		
75th Percentile	NonEst		NonEst, NonEst		

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	120	6	4, (0.007)	0.050	0.023, 0.108
[4-12)	114	18	9, (0.016)	0.150	0.097, 0.227
[12-26)	102	32	17, (0.030)	0.269	0.198, 0.358
[26-40)	86	40	25, (0.044)	0.338	0.260, 0.431
[40-52)	76	46	174, (0.305)	0.390	0.309, 0.484
[52-EoT]	46	46	433, (0.758)	0.390	0.309, 0.484
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	23.29	14.00, 34.86			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	58	3	3, (0.010)	0.052	0.017, 0.154
[4-12)	53	6	5, (0.017)	0.106	0.049, 0.221
[12-26)	50	10	13, (0.045)	0.178	0.100, 0.305
[26-40)	46	14	18, (0.063)	0.251	0.157, 0.387
[40-52)	40	17	93, (0.324)	0.307	0.203, 0.447
[52-EoT]	27	17	240, (0.836)	0.307	0.203, 0.447
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	38.86	17.29, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13e Time to First Severe Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15e Time to First Severe Asthma Exacerbations by Number of exacerbations in the previous year - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Number of Exacerbation in the Previous year: 1						
Number of Patients Included in Model	439	451	229			
Number of Censored Patients	364	359	199			
Treatment				0.052		
Country				0.001**		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.829 [0.611, 1.126]	0.231
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.373 [0.898, 2.099]	0.143
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.604 [0.400, 0.913]	0.017*

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15e Time to First Severe Asthma Exacerbations by Number of exacerbations in the previous year - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Number of Exacerbation in the Previous year: > 1						
Number of Patients Included in Model	132	120	58			
Number of Censored Patients	88	74	41			
Effect						
Treatment				0.575		
Country				0.017*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.967 [0.635, 1.473]	0.875
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.297 [0.735, 2.290]	0.369
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.745 [0.425, 1.305]	0.304

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12f Statistical Analysis of Severe Asthma Exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400]					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.235	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.296 [0.231, 0.378]	0.335 [0.263, 0.428]	0.228 [0.155, 0.335]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.882 [0.633, 1.231] 0.461
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.298 [0.830, 2.030] 0.253
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.680 [0.435, 1.062] 0.090

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12f Statistical Analysis of Severe Asthma Exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.125	
Country				0.012*	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.223 [0.165, 0.303]	0.302 [0.230, 0.395]	0.189 [0.122, 0.293]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.740 [0.498, 1.101] 0.137
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.182 [0.699, 1.997] 0.532
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.626 [0.378, 1.036] 0.069

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Degree of reversibility at screening (delta FEV1): (200-400] mL					
CHF 5993 pMDI HS (N=571)					
[0-4)	299	10	2, (0.004)	0.033	0.018, 0.061
[4-12)	289	27	7, (0.012)	0.091	0.063, 0.130
[12-26)	269	47	13, (0.023)	0.159	0.122, 0.206
[26-40)	246	62	22, (0.039)	0.211	0.169, 0.262
[40-52)	225	70	180, (0.315)	0.239	0.194, 0.292
[52-EoT]	132	70	452, (0.792)	0.239	0.194, 0.292
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	37.00, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	281	11	4, (0.007)	0.039	0.022, 0.070
[4-12)	267	22	9, (0.016)	0.079	0.053, 0.118
[12-26)	252	43	17, (0.030)	0.156	0.118, 0.205
[26-40)	228	59	25, (0.044)	0.216	0.172, 0.270
[40-52)	208	68	174, (0.305)	0.250	0.203, 0.306
[52-EoT]	128	70	433, (0.758)	0.250	0.203, 0.306
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	49.43	32.71, NonEst			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	147	4	3, (0.010)	0.027	0.010, 0.071
[4-12)	140	10	5, (0.017)	0.069	0.038, 0.124
[12-26)	134	13	13, (0.045)	0.090	0.053, 0.150
[26-40)	128	21	18, (0.063)	0.148	0.099, 0.218
[40-52)	116	27	93, (0.324)	0.192	0.136, 0.268
[52-EoT]	77	28	240, (0.836)	0.192	0.136, 0.268
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	52.71	48.14, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Degree of reversibility at screening (delta FEV1): > 400 mL					
CHF 5993 pMDI HS (N=571)					
[0-4)	271	5	2, (0.004)	0.018	0.008, 0.044
[4-12)	264	18	7, (0.012)	0.067	0.043, 0.104
[12-26)	249	32	13, (0.023)	0.120	0.086, 0.165
[26-40)	232	43	22, (0.039)	0.162	0.122, 0.212
[40-52)	218	49	180, (0.315)	0.185	0.143, 0.237
[52-EoT]	139	49	452, (0.792)	0.185	0.143, 0.237
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	290	9	4, (0.007)	0.031	0.016, 0.059
[4-12)	280	27	9, (0.016)	0.094	0.065, 0.133
[12-26)	261	48	17, (0.030)	0.168	0.129, 0.216
[26-40)	235	60	25, (0.044)	0.210	0.167, 0.262
[40-52)	219	68	174, (0.305)	0.239	0.194, 0.293
[52-EoT]	133	68	433, (0.758)	0.239	0.194, 0.293
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	35.00, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	140	3	3, (0.010)	0.021	0.007, 0.065
[4-12)	137	5	5, (0.017)	0.036	0.015, 0.084
[12-26)	133	11	13, (0.045)	0.080	0.045, 0.140
[26-40)	122	17	18, (0.063)	0.126	0.080, 0.195
[40-52)	115	19	93, (0.324)	0.141	0.092, 0.212
[52-EoT]	71	19	240, (0.836)	0.141	0.092, 0.212
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13f Time to First Severe Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15f Time to First Severe Asthma Exacerbations by Degree of reversibility at screening - Cox Proportional Hazards Analysis
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL						
Number of Patients Included in Model	299	281	147			
Number of Censored Patients	229	211	119			
Treatment				0.386		
Country				<0.001***		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.911 [0.654, 1.270]	0.584
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.242 [0.800, 1.927]	0.334
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.734 [0.473, 1.139]	0.168

Produced: 17 December 2020

Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15f Time to First Severe Asthma Exacerbations by Degree of reversibility at screening - Cox Proportional Hazards Analysis
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Degree of reversibility at screening (delta FEV1): > 400 mL						
Number of Patients Included in Model	271	290	140			
Number of Censored Patients	222	222	121			
Effect						
Treatment				0.069		
Country				0.023*		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.778 [0.539, 1.125]	0.182
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.380 [0.812, 2.346]	0.234
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.564 [0.339, 0.938]	0.027*

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12g Statistical Analysis of Severe Asthma Exacerbations stratified by Use of spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of spacer: Yes					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.025*	
Country				0.017*	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.136 [0.000, NE]	0.202 [0.000, NE]	0.090 [0.000, NE]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.673 [0.415, 1.092] 0.109
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.519 [0.784, 2.944] 0.216
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.443 [0.238, 0.824] 0.010*

Produced: 17 December 2020 Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12g Statistical Analysis of Severe Asthma Exacerbations stratified by Use of spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of spacer: No					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.303	
Country				0.003**	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.006**	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.274 [0.221, 0.340]	0.302 [0.244, 0.373]	0.222 [0.159, 0.309]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.909 [0.674, 1.226] 0.533
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.238 [0.835, 1.835] 0.288
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.735 [0.497, 1.087] 0.123

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Use of spacer: Yes					
CHF 5993 pMDI HS (N=571)					
[0-4)	129	3	2, (0.004)	0.023	0.008, 0.070
[4-12)	126	13	7, (0.012)	0.102	0.060, 0.169
[12-26)	114	20	13, (0.023)	0.157	0.105, 0.233
[26-40)	106	25	22, (0.039)	0.197	0.138, 0.278
[40-52)	99	27	180, (0.315)	0.213	0.152, 0.296
[52-EoT]	61	27	452, (0.792)	0.213	0.152, 0.296
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	26.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	138	8	4, (0.007)	0.058	0.030, 0.113
[4-12)	128	18	9, (0.016)	0.132	0.085, 0.201
[12-26)	118	28	17, (0.030)	0.206	0.147, 0.284
[26-40)	106	37	25, (0.044)	0.274	0.206, 0.357
[40-52)	95	41	174, (0.305)	0.304	0.234, 0.390
[52-EoT]	57	41	433, (0.758)	0.304	0.234, 0.390
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	32.71	17.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	74	3	3, (0.010)	0.041	0.013, 0.122
[4-12)	70	3	5, (0.017)	0.041	0.013, 0.122
[12-26)	70	6	13, (0.045)	0.082	0.038, 0.173
[26-40)	67	10	18, (0.063)	0.138	0.077, 0.242
[40-52)	61	12	93, (0.324)	0.167	0.098, 0.275
[52-EoT]	41	12	240, (0.836)	0.167	0.098, 0.275
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	42.43, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Use of spacer: No					
CHF 5993 pMDI HS (N=571)					
[0-4)	442	12	2, (0.004)	0.027	0.016, 0.047
[4-12)	428	32	7, (0.012)	0.073	0.052, 0.101
[12-26)	405	59	13, (0.023)	0.135	0.106, 0.171
[26-40)	373	80	22, (0.039)	0.184	0.151, 0.224
[40-52)	345	92	180, (0.315)	0.213	0.177, 0.255
[52-EoT]	211	92	452, (0.792)	0.213	0.177, 0.255
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	49.57, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	433	12	4, (0.007)	0.028	0.016, 0.048
[4-12)	419	31	9, (0.016)	0.072	0.051, 0.101
[12-26)	395	63	17, (0.030)	0.148	0.118, 0.186
[26-40)	357	82	25, (0.044)	0.194	0.159, 0.235
[40-52)	332	95	174, (0.305)	0.226	0.188, 0.269
[52-EoT]	204	97	433, (0.758)	0.226	0.188, 0.269
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	53.00	44.00, NonEst			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	213	4	3, (0.010)	0.019	0.007, 0.049
[4-12)	207	12	5, (0.017)	0.057	0.033, 0.098
[12-26)	197	18	13, (0.045)	0.086	0.055, 0.133
[26-40)	183	28	18, (0.063)	0.137	0.096, 0.192
[40-52)	170	34	93, (0.324)	0.168	0.123, 0.227
[52-EoT]	107	35	240, (0.836)	0.168	0.123, 0.227
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	52.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Severe Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15g Time to First Severe Asthma Exacerbations by Use of spacer - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Use of spacer: Yes						
Number of Patients Included in Model	129	138	74			
Number of Censored Patients	102	97	62			
Treatment				0.044*		
Country				0.064		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.713 [0.436, 1.168]	0.179
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.589 [0.800, 3.159]	0.186
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.449 [0.234, 0.860]	0.016*

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15g Time to First Severe Asthma Exacerbations by Use of spacer - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Use of spacer: No						
Number of Patients Included in Model	442	433	213			
Number of Censored Patients	350	336	178			
Effect						
Treatment				0.216		
Country				0.007**		
Number of Asthma Exacerbations in Previous Year				0.009**		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.907 [0.682, 1.207]	0.503
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.281 [0.867, 1.893]	0.214
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.708 [0.481, 1.042]	0.080

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12h Statistical Analysis of Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.025*	
Country				0.011*	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.309 [0.240, 0.399]	0.423 [0.337, 0.530]	0.236 [0.158, 0.353]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.732 [0.524, 1.023] 0.067
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.309 [0.818, 2.095] 0.261
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.559 [0.354, 0.883] 0.013*

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12h Statistical Analysis of Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.530	
Country				0.010**	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.223 [0.167, 0.297]	0.241 [0.181, 0.322]	0.182 [0.119, 0.277]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.922 [0.621, 1.369] 0.687
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.224 [0.743, 2.015] 0.427
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.753 [0.460, 1.233] 0.260

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Relevant Concomitant Cardiovascular Diseases: Yes					
CHF 5993 pMDI HS (N=571)					
[0-4)	273	11	2, (0.004)	0.040	0.023, 0.072
[4-12)	262	28	7, (0.012)	0.103	0.073, 0.146
[12-26)	241	42	13, (0.023)	0.156	0.117, 0.205
[26-40)	226	56	22, (0.039)	0.208	0.165, 0.262
[40-52)	207	62	180, (0.315)	0.231	0.185, 0.287
[52-EoT]	129	62	452, (0.792)	0.231	0.185, 0.287
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	37.86, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	287	11	4, (0.007)	0.038	0.022, 0.068
[4-12)	274	34	9, (0.016)	0.120	0.087, 0.163
[12-26)	249	58	17, (0.030)	0.206	0.163, 0.258
[26-40)	220	78	25, (0.044)	0.278	0.230, 0.335
[40-52)	196	83	174, (0.305)	0.297	0.247, 0.354
[52-EoT]	130	85	433, (0.758)	0.297	0.247, 0.354
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	32.71	25.71, 53.00			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	134	2	3, (0.010)	0.015	0.004, 0.058
[4-12)	132	7	5, (0.017)	0.052	0.025, 0.106
[12-26)	127	12	13, (0.045)	0.090	0.052, 0.153
[26-40)	119	21	18, (0.063)	0.159	0.107, 0.234
[40-52)	109	24	93, (0.324)	0.183	0.126, 0.260
[52-EoT]	70	25	240, (0.836)	0.183	0.126, 0.260
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	45.86, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Relevant Concomitant Cardiovascular Diseases: No CHF 5993 pMDI HS (N=571)					
[0-4)	298	4	2, (0.004)	0.013	0.005, 0.035
[4-12)	292	17	7, (0.012)	0.058	0.036, 0.091
[12-26)	278	37	13, (0.023)	0.126	0.093, 0.170
[26-40)	253	49	22, (0.039)	0.168	0.130, 0.216
[40-52)	237	57	180, (0.315)	0.196	0.155, 0.247
[52-EoT]	143	57	452, (0.792)	0.196	0.155, 0.247
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	284	9	4, (0.007)	0.032	0.017, 0.060
[4-12)	273	15	9, (0.016)	0.053	0.032, 0.087
[12-26)	264	33	17, (0.030)	0.118	0.085, 0.162
[26-40)	243	41	25, (0.044)	0.147	0.111, 0.195
[40-52)	231	53	174, (0.305)	0.192	0.150, 0.243
[52-EoT]	131	53	433, (0.758)	0.192	0.150, 0.243
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	153	5	3, (0.010)	0.033	0.014, 0.077
[4-12)	145	8	5, (0.017)	0.053	0.027, 0.103
[12-26)	140	12	13, (0.045)	0.080	0.046, 0.137
[26-40)	131	17	18, (0.063)	0.116	0.074, 0.181
[40-52)	122	22	93, (0.324)	0.153	0.104, 0.223
[52-EoT]	78	22	240, (0.836)	0.153	0.104, 0.223
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13h Time to First Severe Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15h Time to First Severe Asthma Exacerbations by Relevant concomitant cardiovascular disease - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Relevant Concomitant Cardiovascular Diseases: Yes						
Number of Patients Included in Model	273	287	134			
Number of Censored Patients	211	202	109			
Treatment				0.020*		
Country				0.008**		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.714 [0.513, 0.995]	0.046*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.263 [0.793, 2.013]	0.325
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.565 [0.361, 0.886]	0.013*

Produced: 17 December 2020

Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15h Time to First Severe Asthma Exacerbations by Relevant concomitant cardiovascular disease - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Relevant Concomitant Cardiovascular Diseases: No						
Number of Patients Included in Model	298	284	153			
Number of Censored Patients	241	231	131			
Effect						
Treatment				0.477		
Country				0.027*		
Number of Asthma Exacerbations in Previous Year				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.039 [0.713, 1.515]	0.842
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.349 [0.823, 2.210]	0.234
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.770 [0.468, 1.268]	0.305

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.12i Statistical Analysis of Severe Asthma Exacerbations stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.081	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.277 [0.214, 0.357]	0.368 [0.291, 0.463]	0.234 [0.161, 0.341]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.752 [0.535, 1.058] 0.102
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.181 [0.757, 1.842] 0.465
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.637 [0.412, 0.987] 0.043*

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.12i Statistical Analysis of Severe Asthma Exacerbations stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.185	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.007**	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	0.283 [0.211, 0.378]	0.344 [0.261, 0.453]	0.210 [0.132, 0.333]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.822 [0.552, 1.222] 0.332
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.348 [0.780, 2.328] 0.284
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.610 [0.356, 1.045] 0.072

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Region: Europe					
CHF 5993 pMDI HS (N=571)					
[0-4)	319	11	2, (0.004)	0.034	0.019, 0.061
[4-12)	307	29	7, (0.012)	0.092	0.065, 0.129
[12-26)	286	48	13, (0.023)	0.152	0.117, 0.197
[26-40)	263	61	22, (0.039)	0.195	0.155, 0.243
[40-52)	244	71	180, (0.315)	0.228	0.185, 0.279
[52-EoT]	142	71	452, (0.792)	0.228	0.185, 0.279
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	40.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	319	12	4, (0.007)	0.038	0.022, 0.066
[4-12)	304	25	9, (0.016)	0.079	0.054, 0.115
[12-26)	288	47	17, (0.030)	0.150	0.115, 0.195
[26-40)	261	59	25, (0.044)	0.189	0.150, 0.238
[40-52)	245	74	174, (0.305)	0.239	0.196, 0.291
[52-EoT]	142	76	433, (0.758)	0.239	0.196, 0.291
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	53.00	41.14, NonEst			
50th Percentile	NonEst	53.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 2 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	160	4	3, (0.010)	0.025	0.009, 0.065
[4-12)	154	9	5, (0.017)	0.057	0.030, 0.106
[12-26)	148	14	13, (0.045)	0.089	0.054, 0.146
[26-40)	139	23	18, (0.063)	0.149	0.102, 0.216
[40-52)	127	29	93, (0.324)	0.190	0.136, 0.262
[52-EoT]	77	29	240, (0.836)	0.190	0.136, 0.262
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	49.00, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 3 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Region: Rest of World CHF 5993 pMDI HS (N=571)					
[0-4)	252	4	2, (0.004)	0.016	0.006, 0.042
[4-12)	247	16	7, (0.012)	0.064	0.040, 0.102
[12-26)	233	31	13, (0.023)	0.125	0.089, 0.172
[26-40)	216	44	22, (0.039)	0.178	0.135, 0.231
[40-52)	200	48	180, (0.315)	0.194	0.150, 0.249
[52-EoT]	130	48	452, (0.792)	0.194	0.150, 0.249
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	NonEst, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	252	8	4, (0.007)	0.032	0.016, 0.063
[4-12)	243	24	9, (0.016)	0.096	0.065, 0.139
[12-26)	225	44	17, (0.030)	0.177	0.135, 0.231
[26-40)	202	60	25, (0.044)	0.243	0.194, 0.301
[40-52)	182	62	174, (0.305)	0.251	0.202, 0.310
[52-EoT]	119	62	433, (0.758)	0.251	0.202, 0.310
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	45.86	27.86, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 6 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	127	3	3, (0.010)	0.024	0.008, 0.072
[4-12)	123	6	5, (0.017)	0.048	0.022, 0.103
[12-26)	119	10	13, (0.045)	0.081	0.044, 0.145
[26-40)	111	15	18, (0.063)	0.123	0.076, 0.195
[40-52)	104	17	93, (0.324)	0.139	0.089, 0.215
[52-EoT]	71	18	240, (0.836)	0.139	0.089, 0.215
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	NonEst	52.71, NonEst			
50th Percentile	NonEst	NonEst, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 7 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.13i Time to First Severe Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Applicable

Notes: [1] * Severe Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15i Time to First Severe Asthma Exacerbations by Region - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI] p-value
Region: Europe					
Number of Patients Included in Model	319	319	160		
Number of Censored Patients	248	243	131		
Treatment				0.285	
Number of Asthma Exacerbations in Previous Year				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.914 [0.662, 1.264] 0.587
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.292 [0.839, 1.991] 0.245
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.708 [0.461, 1.085] 0.113

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 19.2.15i Time to First Severe Asthma Exacerbations by Region - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Region: Rest of World						
Number of Patients Included in Model	252	252	127			
Number of Censored Patients	204	190	109			
Effect						
Treatment				0.056		
Number of Asthma Exacerbations in Previous Year				0.002**		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.725 [0.497, 1.057]	0.095
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.293 [0.751, 2.226]	0.353
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.561 [0.332, 0.948]	0.031*

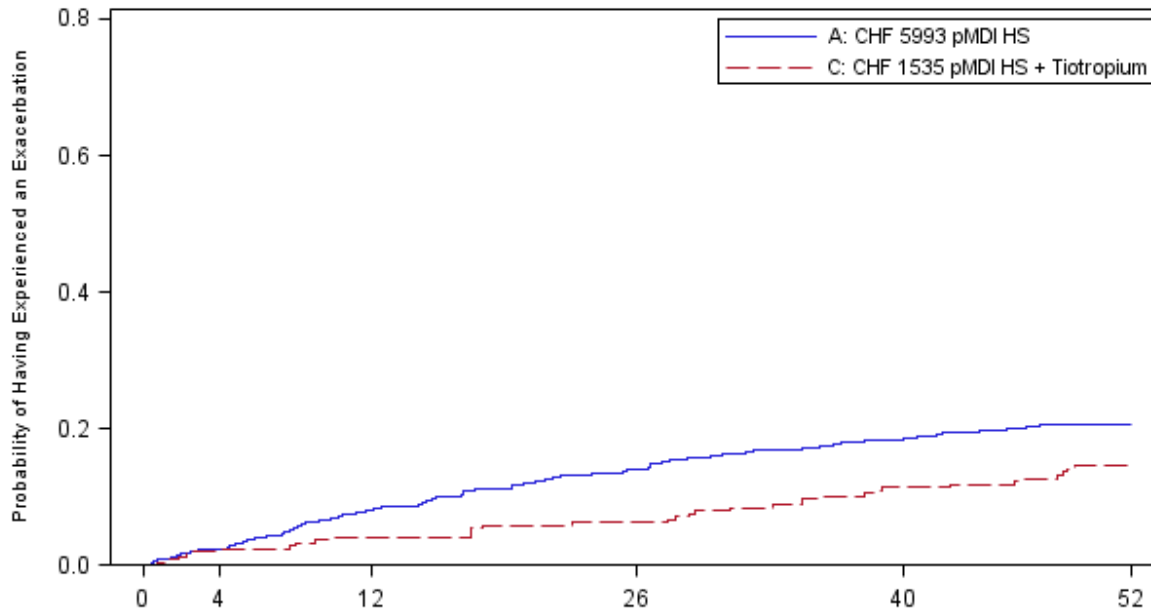
Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Severe Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

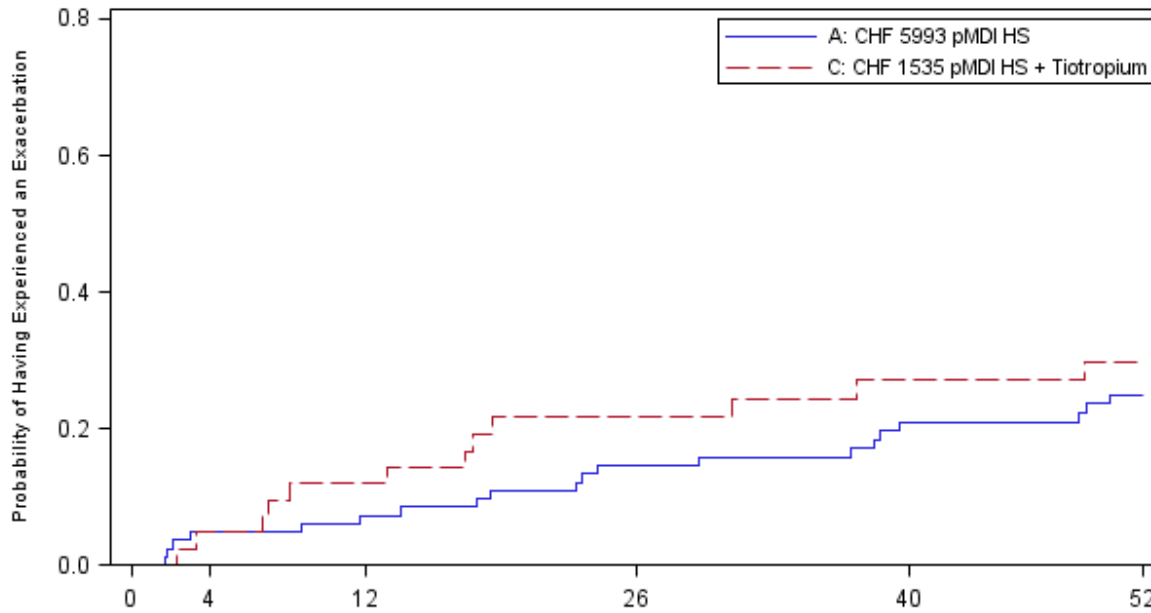
Figure 15.2.16d1 Time to Severe Asthma Exacerbations Stratified by Smoking Status - Kaplan Meier Analysis
 Smoking Status: Non Smoker
 (Intention-to-Treat Population)



Number of Patients at Risk

A:	488	475	443	410	383	235
C:	245	237	230	219	204	129
	Week					

Figure 15.2.16d2 Time to Severe Asthma Exacerbations Stratified by Smoking Status - Kaplan Meier Analysis
 Smoking Status: Ex-Smoker
 (Intention-to-Treat Population)



Number of Patients at Risk

A:	83	79	76	69	61	37
C:	42	40	37	31	27	19
				Week		

ADDITIONAL_TLF_BATCH2_MODERATE_EXACERBATION

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch2

Date of Production: 17/12/2020

Identification Code: Additional_TLF_batch2_Moderate_Exacerbation_CCD-05993AB2-02_20201217(Batch2)

Table 15.2.11a Statistical Analysis of Moderate Asthma Exacerbations
including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.941
Country			0.002**
Number of Asthma Exacerbations in Previous Year (1, >1)			0.157
Age Group			0.162
Age Group Treatment Interaction			0.599

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.11b Statistical Analysis of Moderate Asthma Exacerbations
including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.610
Country			0.004**
Number of Asthma Exacerbations in Previous Year (1, >1)			0.180
Gender			0.534
Gender Treatment Interaction			0.649

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.11c Statistical Analysis of Moderate Asthma Exacerbations
including Bmi - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.813
Country			0.004**
Number of Asthma Exacerbations in Previous Year (1, >1)			0.153
Bmi			0.304
Bmi Treatment Interaction			0.690

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.11d Statistical Analysis of Moderate Asthma Exacerbations including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.840
Country			0.004**
Number of Asthma Exacerbations in Previous Year (1, >1)			0.175
Smoking Status			0.076
Smoking Status Treatment Interaction			0.855

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.11e Statistical Analysis of Moderate Asthma Exacerbations including Number of exacerbations in the previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.287
Country			0.004**
Number of exacerbations in the previous year			0.468
Number of exacerbations in the previous year Treatment Interaction			0.207

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 15.2.11f Statistical Analysis of Moderate Asthma Exacerbations including Degree of reversibility at screening - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.757
Country			0.002**
Number of Asthma Exacerbations in Previous Year (1, >1)			0.136
Degree of reversibility at screening			0.091
Degree of reversibility at screening Treatment Interaction			0.742

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.11g Statistical Analysis of Moderate Asthma Exacerbations including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.247
Country			0.004**
Number of Asthma Exacerbations in Previous Year (1, >1)			0.141
Use of spacer			0.699
Use of spacer Treatment Interaction			0.117

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.11h Statistical Analysis of Moderate Asthma Exacerbations including Relevant concomitant cardiovascular disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.772
Country			0.003**
Number of Asthma Exacerbations in Previous Year (1, >1)			0.164
Relevant concomitant cardiovascular disease			0.124
Relevant concomitant cardiovascular disease Treatment Interaction			0.166

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.11i Statistical Analysis of Moderate Asthma Exacerbations including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.742
Number of Asthma Exacerbations in Previous Year (1, >1)			0.153
Region			0.981
Region Treatment Interaction			0.020*

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.14a Time to First Moderate Asthma Exacerbations including Age Group -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			0.236
Country			0.003**
Number of Asthma Exacerbations in Previous Year			0.115
Age Group			0.779
Age Group Treatment Interaction			0.391

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14b Time to First Moderate Asthma Exacerbations including Gender -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			0.754
Country			0.005**
Number of Asthma Exacerbations in Previous Year			0.151
Gender			0.218
Gender Treatment Interaction			0.231

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14c Time to First Moderate Asthma Exacerbations including Bmi -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			0.935
Country			0.005**
Number of Asthma Exacerbations in Previous Year			0.087
Bmi			0.273
Bmi Treatment Interaction			0.731

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14d Time to First Moderate Asthma Exacerbations including Smoking Status -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			0.161
Country			0.004**
Number of Asthma Exacerbations in Previous Year			0.111
Smoking Status			0.825
Smoking Status Treatment Interaction			0.366

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14e Time to First Moderate Asthma Exacerbations including Number of exacerbations in the previous year -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			0.941
Country			0.004**
Number of exacerbations in the previous year			0.746
Number of exacerbations in the previous year Treatment Interaction			0.500

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment and country as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14f Time to First Moderate Asthma Exacerbations including Degree of reversibility at screening -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	287	137	
Effect			
Treatment			0.481
Country			0.003**
Number of Asthma Exacerbations in Previous Year			0.079
Degree of reversibility at screening			0.041*
Degree of reversibility at screening Treatment Interaction			0.042*

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14g Time to First Moderate Asthma Exacerbations including Use of spacer -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			0.948
Country			0.005**
Number of Asthma Exacerbations in Previous Year			0.133
Use of spacer			0.709
Use of spacer Treatment Interaction			0.587

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14h Time to First Moderate Asthma Exacerbations including Relevant concomitant cardiovascular disease -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			0.409
Country			0.007**
Number of Asthma Exacerbations in Previous Year			0.111
Relevant concomitant cardiovascular disease			0.029*
Relevant concomitant cardiovascular disease Treatment Interaction			0.943

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations

in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.14i Time to First Moderate Asthma Exacerbations including Region -
 Cox Proportional Hazards Analysis Interaction Test
 (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Number of Censored Patients	288	137	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in Previous Year			0.055
Region			<0.001***
Region Treatment Interaction			<0.001***

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment and number of asthma exacerbations as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12a Statistical Analysis of Moderate Asthma Exacerbations stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.401	
Country				0.001**	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.040*	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.493 [1.308, 1.704]	1.619 [1.415, 1.852]	1.388 [1.150, 1.674]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.922 [0.764, 1.113] 0.398
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.076 [0.855, 1.354] 0.534
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.857 [0.680, 1.080] 0.190

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12a Statistical Analysis of Moderate Asthma Exacerbations stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.392	
Country				0.052	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.843	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.049 [0.746, 1.475]	1.440 [1.075, 1.929]	1.175 [0.704, 1.962]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.728 [0.459, 1.156] 0.178
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.892 [0.481, 1.654] 0.717
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.816 [0.452, 1.473] 0.500

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Age Group: <65 years old CHF 5993 pMDI HS (N=571)					
[0-4)	473	85	2, (0.004)	0.180	0.148, 0.218
[4-12)	386	152	6, (0.011)	0.323	0.283, 0.367
[12-26)	316	202	13, (0.023)	0.432	0.388, 0.478
[26-40)	260	230	16, (0.028)	0.493	0.449, 0.539
[40-52)	230	241	111, (0.194)	0.518	0.473, 0.564
[52-EoT]	148	241	288, (0.504)	0.518	0.473, 0.564
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.71	4.86, 9.00			
50th Percentile	47.14	29.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	448	101	3, (0.005)	0.226	0.190, 0.267
[4-12)	345	164	5, (0.009)	0.368	0.325, 0.414
[12-26)	280	216	10, (0.018)	0.485	0.440, 0.533
[26-40)	225	245	16, (0.028)	0.552	0.507, 0.599
[40-52)	193	258	92, (0.161)	0.583	0.537, 0.629
[52-EoT]	123	258	251, (0.440)	0.583	0.537, 0.629
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.86	3.43, 6.71			
50th Percentile	28.14	18.86, 38.71			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	246	51	2, (0.007)	0.208	0.162, 0.264
[4-12)	193	89	4, (0.014)	0.364	0.307, 0.428
[12-26)	154	111	8, (0.028)	0.455	0.395, 0.520
[26-40)	129	122	11, (0.038)	0.502	0.441, 0.567
[40-52)	117	129	53, (0.185)	0.532	0.471, 0.596
[52-EoT]	72	129	137, (0.477)	0.532	0.471, 0.596
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.00	3.29, 8.57			
50th Percentile	38.29	20.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
--------------	--	---	---	---	-------------------------

Treatments	Median difference
CHF 1535 pMDI HS + Tiotropium	10.14
- CHF 1535 pMDI HS	
CHF 5993 pMDI HS - CHF 1535 pMDI HS	19.00
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium	8.86

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Age Group: >= 65 years old					
CHF 5993 pMDI HS (N=571)					
[0-4)	98	11	2, (0.004)	0.112	0.064, 0.194
[4-12)	87	23	6, (0.011)	0.236	0.164, 0.334
[12-26)	74	32	13, (0.023)	0.329	0.245, 0.432
[26-40)	64	39	16, (0.028)	0.403	0.313, 0.507
[40-52)	56	42	111, (0.194)	0.435	0.343, 0.539
[52-EoT]	29	42	288, (0.504)	0.435	0.343, 0.539
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	15.86	7.29, 26.43			
50th Percentile	NonEst	37.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	123	26	3, (0.005)	0.213	0.150, 0.297
[4-12)	96	42	5, (0.009)	0.344	0.267, 0.436
[12-26)	80	54	10, (0.018)	0.444	0.361, 0.537
[26-40)	66	57	16, (0.028)	0.470	0.385, 0.562
[40-52)	60	62	92, (0.161)	0.514	0.428, 0.606
[52-EoT]	36	62	251, (0.440)	0.514	0.428, 0.606
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.00	2.86, 8.14			
50th Percentile	48.29	19.43, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	41	7	2, (0.007)	0.171	0.085, 0.325
[4-12)	34	13	4, (0.014)	0.320	0.200, 0.487
[12-26)	27	16	8, (0.028)	0.399	0.266, 0.567
[26-40)	23	16	11, (0.038)	0.399	0.266, 0.567
[40-52)	21	21	53, (0.185)	0.542	0.393, 0.705
[52-EoT]	12	21	137, (0.477)	0.542	0.393, 0.705
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.86	2.29, 25.57			
50th Percentile	49.86	12.86, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13a Time to First Moderate Asthma Exacerbations stratified by Age Group - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium	1.57				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15a Time to First Moderate Asthma Exacerbations by Age Group - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Age Group: <65 years old						
Number of Patients Included in Model	473	448	246			
Number of Censored Patients	232	190	117			
Treatment				0.065		
Country				<0.001***		
Number of Asthma Exacerbations in Previous Year				0.014*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.812 [0.681, 0.968]	0.020*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.920 [0.743, 1.140]	0.447
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.882 [0.714, 1.090]	0.245

Produced: 17 December 2020 Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15a Time to First Moderate Asthma Exacerbations by Age Group - Cox Proportional Hazards Analysis
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Number of Censored Patients	56	61	20		
Effect					
Treatment				0.326	
Country				0.290	
Number of Asthma Exacerbations in Previous Year				0.726	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.781 [0.523, 1.166] 0.226
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.694 [0.405, 1.191] 0.185
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.125 [0.675, 1.875] 0.652

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12b Statistical Analysis of Moderate Asthma Exacerbations stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.441	
Country				0.031*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.275	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.350 [1.090, 1.671]	1.569 [1.289, 1.909]	1.277 [0.933, 1.746]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.861 [0.644, 1.150] 0.310
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.057 [0.722, 1.548] 0.775
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.814 [0.562, 1.179] 0.277

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12b Statistical Analysis of Moderate Asthma Exacerbations stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.647	
Country				0.005**	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.098	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.450 [1.247, 1.687]	1.590 [1.361, 1.858]	1.441 [1.162, 1.787]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.912 [0.734, 1.133] 0.405
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.006 [0.773, 1.311] 0.962
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.906 [0.695, 1.181] 0.466

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Gender: Male					
CHF 5993 pMDI HS (N=571)					
[0-4)	212	40	2, (0.004)	0.189	0.142, 0.249
[4-12)	171	70	6, (0.011)	0.332	0.273, 0.400
[12-26)	140	88	13, (0.023)	0.418	0.355, 0.488
[26-40)	120	100	16, (0.028)	0.477	0.411, 0.546
[40-52)	107	105	111, (0.194)	0.501	0.436, 0.571
[52-EoT]	65	105	288, (0.504)	0.501	0.436, 0.571
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.00	4.00, 9.57			
50th Percentile	50.86	26.43, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	244	51	3, (0.005)	0.210	0.164, 0.267
[4-12)	192	85	5, (0.009)	0.350	0.293, 0.413
[12-26)	158	110	10, (0.018)	0.453	0.393, 0.518
[26-40)	131	125	16, (0.028)	0.516	0.455, 0.580
[40-52)	114	128	92, (0.161)	0.529	0.467, 0.593
[52-EoT]	73	128	251, (0.440)	0.529	0.467, 0.593
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.14	3.43, 7.14			
50th Percentile	33.71	21.00, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	103	16	2, (0.007)	0.155	0.098, 0.241
[4-12)	86	30	4, (0.014)	0.294	0.216, 0.393
[12-26)	71	42	8, (0.028)	0.413	0.325, 0.515
[26-40)	58	45	11, (0.038)	0.445	0.354, 0.547
[40-52)	53	48	53, (0.185)	0.477	0.384, 0.579
[52-EoT]	31	48	137, (0.477)	0.477	0.384, 0.579
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	9.43	4.14, 12.86			
50th Percentile	NonEst	21.00, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS	17.14				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Gender: Female					
CHF 5993 pMDI HS (N=571)					
[0-4)	359	56	2, (0.004)	0.156	0.122, 0.198
[4-12)	302	105	6, (0.011)	0.294	0.250, 0.344
[12-26)	250	146	13, (0.023)	0.412	0.362, 0.465
[26-40)	204	169	16, (0.028)	0.478	0.427, 0.532
[40-52)	179	178	111, (0.194)	0.505	0.454, 0.558
[52-EoT]	112	178	288, (0.504)	0.505	0.454, 0.558
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	8.71	6.00, 12.00			
50th Percentile	48.43	31.29, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	327	76	3, (0.005)	0.233	0.191, 0.283
[4-12)	249	121	5, (0.009)	0.372	0.322, 0.427
[12-26)	202	160	10, (0.018)	0.494	0.441, 0.550
[26-40)	160	177	16, (0.028)	0.549	0.495, 0.604
[40-52)	139	192	92, (0.161)	0.598	0.544, 0.652
[52-EoT]	86	192	251, (0.440)	0.598	0.544, 0.652
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.86	2.86, 7.43			
50th Percentile	27.14	17.71, 41.86			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	184	42	2, (0.007)	0.229	0.175, 0.297
[4-12)	141	72	4, (0.014)	0.394	0.327, 0.469
[12-26)	110	85	8, (0.028)	0.467	0.397, 0.542
[26-40)	94	93	11, (0.038)	0.513	0.442, 0.587
[40-52)	85	102	53, (0.185)	0.564	0.493, 0.638
[52-EoT]	53	102	137, (0.477)	0.564	0.493, 0.638
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.14	2.71, 7.29			
50th Percentile	34.29	16.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13b Time to First Moderate Asthma Exacerbations stratified by Gender - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments					
CHF 1535 pMDI HS + Tiotropium	Median difference				
- CHF 1535 pMDI HS	7.14				
CHF 5993 pMDI HS - CHF 1535 pMDI HS	21.29				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium	14.14				

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15b Time to First Moderate Asthma Exacerbations by Gender - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Gender: Male						
Number of Patients Included in Model	212	244	103			
Number of Censored Patients	107	116	55			
Treatment				0.465		
Country				0.001**		
Number of Asthma Exacerbations in Previous Year				0.045*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.870 [0.672, 1.127]	0.292
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.027 [0.729, 1.447]	0.879
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.847 [0.607, 1.182]	0.329

Produced: 17 December 2020 Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15b Time to First Moderate Asthma Exacerbations by Gender - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Gender: Female						
Number of Patients Included in Model	359	327	184			
Number of Censored Patients	181	135	82			
Effect						
Treatment				0.028*		
Country				0.007**		
Number of Asthma Exacerbations in Previous Year				0.174		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.762 [0.621, 0.935]	0.009**
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.814 [0.638, 1.039]	0.098
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.936 [0.735, 1.191]	0.589

Produced: 17 December 2020 Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12c Statistical Analysis of Moderate Asthma Exacerbations stratified by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.575	
Country				0.101	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.911	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.203 [0.925, 1.565]	1.458 [1.146, 1.856]	1.324 [0.912, 1.921]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.825 [0.576, 1.181] 0.293
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.909 [0.574, 1.439] 0.683
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.908 [0.582, 1.415] 0.669

Produced: 17 December 2020

Page 1 of 3

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12c Statistical Analysis of Moderate Asthma Exacerbations stratified by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.498	
Country				0.003**	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.035*	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.349 [1.105, 1.646]	1.507 [1.228, 1.849]	1.225 [0.916, 1.639]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.895 [0.673, 1.191] 0.448
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.101 [0.773, 1.568] 0.594
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.813 [0.569, 1.162] 0.255

Produced: 17 December 2020

Page 2 of 3

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12c Statistical Analysis of Moderate Asthma Exacerbations stratified by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.738	
Country				0.100	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.277	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.608 [1.324, 1.953]	1.719 [1.417, 2.085]	1.507 [1.140, 1.993]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.936 [0.712, 1.230] 0.634
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.067 [0.758, 1.501] 0.711
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.877 [0.624, 1.233] 0.450

Produced: 17 December 2020

Page 3 of 3

Source: Listing 16.2.6.2.3

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
BMI Class: < 25					
CHF 5993 pMDI HS (N=571)					
[0-4)	150	21	2, (0.004)	0.140	0.094, 0.207
[4-12)	128	41	6, (0.011)	0.275	0.211, 0.355
[12-26)	107	54	13, (0.023)	0.365	0.293, 0.449
[26-40)	90	59	16, (0.028)	0.401	0.326, 0.485
[40-52)	85	62	111, (0.194)	0.422	0.347, 0.506
[52-EoT]	59	62	288, (0.504)	0.422	0.347, 0.506
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	9.86	7.00, 17.00			
50th Percentile	NonEst	47.43, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	163	34	3, (0.005)	0.209	0.154, 0.279
[4-12)	129	57	5, (0.009)	0.350	0.282, 0.428
[12-26)	106	77	10, (0.018)	0.472	0.399, 0.552
[26-40)	85	88	16, (0.028)	0.542	0.467, 0.620
[40-52)	71	91	92, (0.161)	0.562	0.487, 0.639
[52-EoT]	48	91	251, (0.440)	0.562	0.487, 0.639
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.43	2.71, 8.86			
50th Percentile	33.29	17.14, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	73	10	2, (0.007)	0.137	0.076, 0.240
[4-12)	63	24	4, (0.014)	0.329	0.234, 0.449
[12-26)	49	29	8, (0.028)	0.398	0.296, 0.520
[26-40)	42	32	11, (0.038)	0.444	0.338, 0.567
[40-52)	36	35	53, (0.185)	0.492	0.382, 0.614
[52-EoT]	24	35	137, (0.477)	0.492	0.382, 0.614
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	8.71	4.29, 13.29			
50th Percentile	NonEst	17.86, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
--------------	--	---	---	---	-------------------------

Treatments Median difference
 CHF 1535 pMDI HS + Tiotropium
 - CHF 1535 pMDI HS
 CHF 5993 pMDI HS - CHF 1535 pMDI HS
 CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium

Produced: 17 December 2020 Page 4 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
BMI Class: [25-30)					
CHF 5993 pMDI HS (N=571)					
[0-4)	217	36	2, (0.004)	0.166	0.123, 0.223
[4-12)	180	70	6, (0.011)	0.324	0.266, 0.391
[12-26)	145	99	13, (0.023)	0.459	0.396, 0.528
[26-40)	116	107	16, (0.028)	0.497	0.432, 0.565
[40-52)	108	108	111, (0.194)	0.501	0.437, 0.570
[52-EoT]	67	108	288, (0.504)	0.501	0.437, 0.570
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	7.14	4.57, 10.71			
50th Percentile	50.43	20.86, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	205	45	3, (0.005)	0.221	0.170, 0.285
[4-12)	158	71	5, (0.009)	0.350	0.289, 0.420
[12-26)	130	94	10, (0.018)	0.467	0.400, 0.538
[26-40)	104	108	16, (0.028)	0.539	0.471, 0.609
[40-52)	88	112	92, (0.161)	0.560	0.492, 0.630
[52-EoT]	56	112	251, (0.440)	0.560	0.492, 0.630
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.14	3.00, 8.14			
50th Percentile	30.29	17.71, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	112	23	2, (0.007)	0.206	0.142, 0.294
[4-12)	87	42	4, (0.014)	0.382	0.298, 0.480
[12-26)	66	49	8, (0.028)	0.449	0.361, 0.547
[26-40)	57	51	11, (0.038)	0.468	0.379, 0.566
[40-52)	55	54	53, (0.185)	0.497	0.407, 0.595
[52-EoT]	31	54	137, (0.477)	0.497	0.407, 0.595
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.14	3.14, 7.43			
50th Percentile	NonEst	16.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
--------------	---	--	--	--	-------------------------------

Treatments	Median difference
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS	
CHF 5993 pMDI HS - CHF 1535 pMDI HS	20.14
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium	

Produced: 17 December 2020 Page 8 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
BMI Class: >=30					
CHF 5993 pMDI HS (N=571)					
[0-4)	204	39	2, (0.004)	0.191	0.144, 0.252
[4-12)	165	64	6, (0.011)	0.315	0.256, 0.384
[12-26)	138	81	13, (0.023)	0.401	0.337, 0.472
[26-40)	118	103	16, (0.028)	0.514	0.447, 0.585
[40-52)	93	113	111, (0.194)	0.567	0.499, 0.637
[52-EoT]	51	113	288, (0.504)	0.567	0.499, 0.637
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.00	3.00, 11.00			
50th Percentile	37.57	28.71, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 9 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	203	48	3, (0.005)	0.237	0.184, 0.301
[4-12)	154	78	5, (0.009)	0.385	0.322, 0.456
[12-26)	124	99	10, (0.018)	0.490	0.423, 0.561
[26-40)	102	106	16, (0.028)	0.525	0.458, 0.595
[40-52)	94	117	92, (0.161)	0.581	0.514, 0.650
[52-EoT]	55	117	251, (0.440)	0.581	0.514, 0.650
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.43	1.86, 6.86			
50th Percentile	30.71	17.00, 49.71			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 10 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	102	25	2, (0.007)	0.245	0.173, 0.341
[4-12)	77	36	4, (0.014)	0.353	0.269, 0.454
[12-26)	66	49	8, (0.028)	0.480	0.389, 0.581
[26-40)	53	55	11, (0.038)	0.539	0.446, 0.638
[40-52)	47	61	53, (0.185)	0.598	0.505, 0.693
[52-EoT]	29	61	137, (0.477)	0.598	0.505, 0.693
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.86	2.14, 9.57			
50th Percentile	33.93	13.00, 51.00			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 11 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13c Time to First Moderate Asthma Exacerbations stratified by Bmi - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments					
CHF 1535 pMDI HS + Tiotropium	Median difference 3.21				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS	6.86				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium	3.64				

Produced: 17 December 2020 Page 12 of 12

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15c Time to First Moderate Asthma Exacerbations by Bmi - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
BMI Class: < 25						
Number of Patients Included in Model	150	163	73			
Number of Censored Patients	88	72	38			
Treatment				0.056		
Country				0.002**		
Number of Asthma Exacerbations in Previous Year				0.751		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.673 [0.486, 0.932]	0.017*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.834 [0.549, 1.266]	0.393
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.807 [0.544, 1.196]	0.285

Produced: 17 December 2020 Page 1 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15c Time to First Moderate Asthma Exacerbations by Bmi - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
BMI Class: [25-30)						
Number of Patients Included in Model	217	205	112			
Number of Censored Patients	109	93	58			
Treatment				0.287		
Country				0.016*		
Number of Asthma Exacerbations in Previous Year				0.032*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.818 [0.625, 1.070]	0.142
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.992 [0.714, 1.379]	0.963
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.824 [0.592, 1.148]	0.253

Produced: 17 December 2020 Page 2 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15c Time to First Moderate Asthma Exacerbations by Bmi - Cox Proportional Hazards Analysis
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	203	102		
Number of Censored Patients	91	86	41		
Effect					
Treatment				0.553	
Country				0.332	
Number of Asthma Exacerbations in Previous Year				0.038*	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.890 [0.687, 1.154] 0.381
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.858 [0.628, 1.174] 0.339
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.037 [0.761, 1.415] 0.817

Produced: 17 December 2020

Page 3 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12d Statistical Analysis of Moderate Asthma Exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.363	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.383	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.370 [1.197, 1.569]	1.512 [1.323, 1.727]	1.290 [1.061, 1.568]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.907 [0.750, 1.096] 0.311
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.062 [0.838, 1.347] 0.617
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.853 [0.674, 1.081] 0.188

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12d Statistical Analysis of Moderate Asthma Exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.884	
Country				0.722	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.005**	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.690 [1.260, 2.266]	1.857 [1.386, 2.488]	1.867 [1.235, 2.825]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.910 [0.600, 1.380] 0.657
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.905 [0.542, 1.510] 0.702
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.006 [0.603, 1.677] 0.983

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Smoking Status: Non smoker CHF 5993 pMDI HS (N=571)					
[0-4)	488	82	2, (0.004)	0.168	0.138, 0.205
[4-12)	404	145	6, (0.011)	0.299	0.260, 0.342
[12-26)	337	197	13, (0.023)	0.408	0.366, 0.454
[26-40)	278	227	16, (0.028)	0.472	0.429, 0.518
[40-52)	247	236	111, (0.194)	0.492	0.448, 0.537
[52-EoT]	153	236	288, (0.504)	0.492	0.448, 0.537
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	8.43	5.86, 10.71			
50th Percentile	NonEst	34.43, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	491	108	3, (0.005)	0.221	0.187, 0.260
[4-12)	380	171	5, (0.009)	0.350	0.309, 0.394
[12-26)	316	229	10, (0.018)	0.470	0.427, 0.515
[26-40)	255	254	16, (0.028)	0.522	0.479, 0.567
[40-52)	226	266	92, (0.161)	0.548	0.504, 0.593
[52-EoT]	146	266	251, (0.440)	0.548	0.504, 0.593
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.14	3.43, 7.57			
50th Percentile	33.71	21.43, 49.71			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	245	49	2, (0.007)	0.200	0.155, 0.256
[4-12)	194	84	4, (0.014)	0.346	0.290, 0.409
[12-26)	157	108	8, (0.028)	0.446	0.386, 0.511
[26-40)	131	118	11, (0.038)	0.489	0.428, 0.554
[40-52)	120	130	53, (0.185)	0.540	0.479, 0.605
[52-EoT]	72	130	137, (0.477)	0.540	0.479, 0.605
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.14	3.71, 9.43			
50th Percentile	46.00	21.00, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium	12.29				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS					
CHF 5993 pMDI HS - CHF 1535					
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Smoking Status: Ex-smoker CHF 5993 pMDI HS (N=571)					
[0-4)	83	14	2, (0.004)	0.169	0.104, 0.268
[4-12)	69	30	6, (0.011)	0.361	0.269, 0.475
[12-26)	53	37	13, (0.023)	0.446	0.347, 0.559
[26-40)	46	42	16, (0.028)	0.508	0.406, 0.619
[40-52)	39	47	111, (0.194)	0.572	0.468, 0.681
[52-EoT]	24	47	288, (0.504)	0.572	0.468, 0.681
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.43	3.29, 10.43			
50th Percentile	39.00	15.43, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	80	19	3, (0.005)	0.237	0.159, 0.347
[4-12)	61	35	5, (0.009)	0.441	0.340, 0.556
[12-26)	44	41	10, (0.018)	0.518	0.413, 0.631
[26-40)	36	48	16, (0.028)	0.614	0.507, 0.722
[40-52)	27	54	92, (0.161)	0.700	0.594, 0.799
[52-EoT]	13	54	251, (0.440)	0.700	0.594, 0.799
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.29	1.71, 5.43			
50th Percentile	22.71	7.43, 36.71			
75th Percentile	NonEst	48.29, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	42	9	2, (0.007)	0.214	0.118, 0.371
[4-12)	33	18	4, (0.014)	0.429	0.296, 0.591
[12-26)	24	19	8, (0.028)	0.453	0.318, 0.615
[26-40)	21	20	11, (0.038)	0.482	0.343, 0.643
[40-52)	18	20	53, (0.185)	0.482	0.343, 0.643
[52-EoT]	12	20	137, (0.477)	0.482	0.343, 0.643
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.86	0.86, 7.86			
50th Percentile	NonEst	7.29, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13d Time to First Moderate Asthma Exacerbations stratified by Smoking Status - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments					
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS	16.29				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15d Time to First Moderate Asthma Exacerbations by Smoking Status - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Smoking Status: Non smoker						
Number of Patients Included in Model	488	491	245			
Number of Censored Patients	252	225	115			
Treatment				0.103		
Country				<0.001***		
Number of Asthma Exacerbations in Previous Year				0.286		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.830 [0.696, 0.990]	0.038*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.863 [0.697, 1.070]	0.180
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.962 [0.779, 1.186]	0.715

Produced: 17 December 2020 Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15d Time to First Moderate Asthma Exacerbations by Smoking Status - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Smoking Status: Ex-smoker						
Number of Patients Included in Model	83	80	42			
Number of Censored Patients	36	26	22			
Effect						
Treatment				0.256		
Country				0.995		
Number of Asthma Exacerbations in Previous Year				0.001**		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.758 [0.509, 1.128]	0.172
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.091 [0.646, 1.843]	0.745
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.695 [0.413, 1.170]	0.171

Produced: 17 December 2020 Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12e Statistical Analysis of Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	451	229		
Effect					
Treatment				0.397	
Country				<0.001***	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.343 [1.163, 1.551]	1.537 [1.336, 1.767]	1.385 [1.134, 1.692]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.874 [0.715, 1.068] 0.188
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.970 [0.757, 1.241] 0.807
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.901 [0.706, 1.151] 0.405

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 15.2.12e Statistical Analysis of Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.388	
Country				0.360	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.692 [1.331, 2.152]	1.756 [1.369, 2.252]	1.286 [0.876, 1.887]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.964 [0.679, 1.369] 0.837
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.316 [0.833, 2.079] 0.239
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.732 [0.464, 1.157] 0.181

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Number of Exacerbation in the Previous year: 1					
CHF 5993 pMDI HS (N=571)					
[0-4)	439	70	2, (0.004)	0.160	0.128, 0.197
[4-12)	368	129	6, (0.011)	0.295	0.255, 0.340
[12-26)	306	172	13, (0.023)	0.395	0.351, 0.443
[26-40)	258	198	16, (0.028)	0.456	0.411, 0.505
[40-52)	230	209	111, (0.194)	0.483	0.437, 0.531
[52-EoT]	141	209	288, (0.504)	0.483	0.437, 0.531
Percentile	Estimates (Weeks)		95% CI		
25th Percentile	8.71		5.57, 11.00		
50th Percentile	NonEst		38.71, NonEst		
75th Percentile	NonEst		NonEst, NonEst		

Produced: 17 December 2020 Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	451	98	3, (0.005)	0.218	0.183, 0.259
[4-12)	350	158	5, (0.009)	0.353	0.310, 0.399
[12-26)	288	204	10, (0.018)	0.457	0.412, 0.504
[26-40)	237	233	16, (0.028)	0.524	0.478, 0.571
[40-52)	203	248	92, (0.161)	0.559	0.513, 0.606
[52-EoT]	127	248	251, (0.440)	0.559	0.513, 0.606
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.29	3.71, 7.71			
50th Percentile	33.71	24.14, 48.43			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	229	43	2, (0.007)	0.188	0.143, 0.245
[4-12)	185	78	4, (0.014)	0.343	0.285, 0.408
[12-26)	148	99	8, (0.028)	0.437	0.375, 0.504
[26-40)	123	109	11, (0.038)	0.484	0.421, 0.551
[40-52)	110	120	53, (0.185)	0.536	0.472, 0.603
[52-EoT]	66	120	137, (0.477)	0.536	0.472, 0.603
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.29	4.14, 9.43			
50th Percentile	46.57	25.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium	12.86				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Number of Exacerbation in the Previous year: > 1 CHF 5993 pMDI HS (N=571)					
[0-4)	132	26	2, (0.004)	0.198	0.139, 0.276
[4-12)	105	46	6, (0.011)	0.352	0.277, 0.440
[12-26)	84	62	13, (0.023)	0.477	0.395, 0.566
[26-40)	66	71	16, (0.028)	0.549	0.465, 0.636
[40-52)	56	74	111, (0.194)	0.573	0.489, 0.659
[52-EoT]	36	74	288, (0.504)	0.573	0.489, 0.659
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.29	2.29, 8.86			
50th Percentile	28.29	17.71, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	120	29	3, (0.005)	0.242	0.175, 0.329
[4-12)	91	48	5, (0.009)	0.400	0.319, 0.493
[12-26)	72	66	10, (0.018)	0.550	0.464, 0.640
[26-40)	54	69	16, (0.028)	0.575	0.489, 0.665
[40-52)	50	72	92, (0.161)	0.601	0.515, 0.689
[52-EoT]	32	72	251, (0.440)	0.601	0.515, 0.689
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.07	1.57, 6.00			
50th Percentile	17.00	12.43, 45.00			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	58	15	2, (0.007)	0.261	0.166, 0.395
[4-12)	42	24	4, (0.014)	0.419	0.304, 0.557
[12-26)	33	28	8, (0.028)	0.490	0.369, 0.625
[26-40)	29	29	11, (0.038)	0.507	0.386, 0.642
[40-52)	28	30	53, (0.185)	0.525	0.403, 0.658
[52-EoT]	18	30	137, (0.477)	0.525	0.403, 0.658
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	3.86	1.29, 8.71			
50th Percentile	34.86	8.71, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13e Time to First Moderate Asthma Exacerbations stratified by Number of exacerbations in the previous year - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium	17.86				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS	11.29				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium	-6.57				

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15e Time to First Moderate Asthma Exacerbations by Number of exacerbations in the previous year - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Number of Exacerbation in the Previous year: 1						
Number of Patients Included in Model	439	451	229			
Number of Censored Patients	230	203	109			
Treatment				0.063		
Country				<0.001***		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.803 [0.668, 0.966]	0.020*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.857 [0.685, 1.074]	0.181
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.937 [0.753, 1.166]	0.558

Produced: 17 December 2020 Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15e Time to First Moderate Asthma Exacerbations by Number of exacerbations in the previous year - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Number of Exacerbation in the Previous year: > 1						
Number of Patients Included in Model	132	120	58			
Number of Censored Patients	58	48	28			
Effect						
Treatment				0.290		
Country				0.125		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.782 [0.562, 1.089]	0.146
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.007 [0.655, 1.549]	0.974
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.776 [0.501, 1.203]	0.258

Produced: 17 December 2020 Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12f Statistical Analysis of Moderate Asthma Exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400]					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.827	
Country				0.007**	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.286	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.580 [1.342, 1.861]	1.523 [1.284, 1.807]	1.443 [1.134, 1.836]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.037 [0.819, 1.314] 0.760
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.095 [0.818, 1.466] 0.541
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.947 [0.705, 1.273] 0.719

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12f Statistical Analysis of Moderate Asthma Exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.134	
Country				0.011*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.110	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.270 [1.053, 1.531]	1.610 [1.352, 1.917]	1.272 [0.980, 1.650]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.789 [0.610, 1.019] 0.070
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.999 [0.724, 1.377] 0.994
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.790 [0.577, 1.080] 0.140

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Degree of reversibility at screening (delta FEV1): (200-400] mL					
CHF 5993 pMDI HS (N=571)					
[0-4)	299	46	2, (0.004)	0.154	0.118, 0.200
[4-12)	253	85	6, (0.011)	0.285	0.238, 0.340
[12-26)	211	120	13, (0.023)	0.406	0.352, 0.464
[26-40)	171	140	16, (0.028)	0.476	0.420, 0.534
[40-52)	149	145	111, (0.194)	0.493	0.438, 0.552
[52-EoT]	87	145	288, (0.504)	0.493	0.438, 0.552
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	8.71	5.57, 13.29			
50th Percentile	NonEst	30.86, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	281	60	3, (0.005)	0.215	0.171, 0.268
[4-12)	218	108	5, (0.009)	0.388	0.334, 0.448
[12-26)	168	141	10, (0.018)	0.509	0.451, 0.569
[26-40)	133	155	16, (0.028)	0.561	0.503, 0.620
[40-52)	116	163	92, (0.161)	0.592	0.534, 0.650
[52-EoT]	76	163	251, (0.440)	0.592	0.534, 0.650
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.14	2.86, 7.14			
50th Percentile	22.71	17.57, 38.71			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	147	32	2, (0.007)	0.219	0.160, 0.295
[4-12)	113	58	4, (0.014)	0.398	0.324, 0.483
[12-26)	87	71	8, (0.028)	0.489	0.411, 0.573
[26-40)	72	79	11, (0.038)	0.548	0.468, 0.631
[40-52)	62	85	53, (0.185)	0.592	0.513, 0.673
[52-EoT]	36	85	137, (0.477)	0.592	0.513, 0.673
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.86	3.29, 6.71			
50th Percentile	30.00	12.86, 49.86			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium	7.29				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Degree of reversibility at screening (delta FEV1): > 400 mL					
CHF 5993 pMDI HS (N=571)					
[0-4)	271	50	2, (0.004)	0.185	0.144, 0.237
[4-12)	219	90	6, (0.011)	0.334	0.282, 0.394
[12-26)	178	114	13, (0.023)	0.425	0.368, 0.486
[26-40)	152	129	16, (0.028)	0.482	0.424, 0.543
[40-52)	136	138	111, (0.194)	0.516	0.458, 0.578
[52-EoT]	89	138	288, (0.504)	0.516	0.458, 0.578
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.71	4.43, 9.57			
50th Percentile	47.71	27.71, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	290	67	3, (0.005)	0.231	0.187, 0.284
[4-12)	223	98	5, (0.009)	0.338	0.287, 0.396
[12-26)	192	129	10, (0.018)	0.446	0.391, 0.505
[26-40)	158	147	16, (0.028)	0.509	0.453, 0.568
[40-52)	137	157	92, (0.161)	0.545	0.489, 0.604
[52-EoT]	83	157	251, (0.440)	0.545	0.489, 0.604
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.57	3.43, 7.57			
50th Percentile	36.86	24.14, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	140	26	2, (0.007)	0.186	0.130, 0.261
[4-12)	114	44	4, (0.014)	0.316	0.246, 0.400
[12-26)	94	56	8, (0.028)	0.404	0.328, 0.491
[26-40)	80	59	11, (0.038)	0.427	0.349, 0.513
[40-52)	76	65	53, (0.185)	0.472	0.392, 0.559
[52-EoT]	48	65	137, (0.477)	0.472	0.392, 0.559
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	7.86	3.00, 12.14			
50th Percentile	NonEst	34.86, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13f Time to First Moderate Asthma Exacerbations stratified by Degree of reversibility at screening - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments					
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS	10.86				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15f Time to First Moderate Asthma Exacerbations by Degree of reversibility at screening - Cox Proportional Hazards Analysis
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL						
Number of Patients Included in Model	299	281	147			
Number of Censored Patients	154	118	62			
Treatment				0.007**		
Country				0.001**		
Number of Asthma Exacerbations in Previous Year				0.125		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.717 [0.572, 0.897]	0.004**
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.717 [0.548, 0.939]	0.016*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.999 [0.768, 1.299]	0.993

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15f Time to First Moderate Asthma Exacerbations by Degree of reversibility at screening - Cox Proportional Hazards Analysis
(Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Degree of reversibility at screening (delta FEV1): > 400 mL						
Number of Patients Included in Model	271	290	140			
Number of Censored Patients	133	133	75			
Effect						
Treatment				0.320		
Country				<0.001***		
Number of Asthma Exacerbations in Previous Year				0.062		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.898 [0.714, 1.130]	0.358
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.115 [0.830, 1.498]	0.472
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.806 [0.602, 1.078]	0.145

Produced: 17 December 2020 Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12g Statistical Analysis of Moderate Asthma Exacerbations stratified by Use of spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of spacer: Yes					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.131	
Country				0.012*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.086	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.457 [1.135, 1.870]	1.550 [1.221, 1.968]	1.008 [0.706, 1.438]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.940 [0.665, 1.328] 0.725
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.446 [0.934, 2.238] 0.098
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.650 [0.424, 0.997] 0.049*

Produced: 17 December 2020 Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12g Statistical Analysis of Moderate Asthma Exacerbations stratified by Use of spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of spacer: No					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.602	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.231	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.412 [1.226, 1.626]	1.563 [1.358, 1.799]	1.463 [1.192, 1.796]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.904 [0.740, 1.103] 0.318
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.965 [0.752, 1.239] 0.779
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.936 [0.731, 1.200] 0.604

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Use of spacer: Yes					
CHF 5993 pMDI HS (N=571)					
[0-4)	129	18	2, (0.004)	0.140	0.090, 0.212
[4-12)	111	39	6, (0.011)	0.305	0.233, 0.393
[12-26)	88	49	13, (0.023)	0.385	0.306, 0.475
[26-40)	77	59	16, (0.028)	0.465	0.383, 0.556
[40-52)	66	63	111, (0.194)	0.498	0.414, 0.588
[52-EoT]	39	63	288, (0.504)	0.498	0.414, 0.588
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	7.86	5.00, 15.43			
50th Percentile	NonEst	28.29, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	138	36	3, (0.005)	0.262	0.197, 0.344
[4-12)	101	53	5, (0.009)	0.386	0.311, 0.473
[12-26)	84	70	10, (0.018)	0.512	0.431, 0.598
[26-40)	65	76	16, (0.028)	0.557	0.476, 0.642
[40-52)	59	83	92, (0.161)	0.610	0.529, 0.692
[52-EoT]	37	83	251, (0.440)	0.610	0.529, 0.692
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	3.71	1.43, 6.00			
50th Percentile	20.29	14.57, 48.43			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	74	15	2, (0.007)	0.204	0.128, 0.316
[4-12)	58	23	4, (0.014)	0.314	0.221, 0.434
[12-26)	50	29	8, (0.028)	0.396	0.295, 0.518
[26-40)	44	33	11, (0.038)	0.452	0.347, 0.573
[40-52)	39	36	53, (0.185)	0.495	0.387, 0.614
[52-EoT]	28	36	137, (0.477)	0.495	0.387, 0.614
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	7.86	3.00, 16.00			
50th Percentile	NonEst	20.71, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Use of spacer: No					
CHF 5993 pMDI HS (N=571)					
[0-4)	442	78	2, (0.004)	0.177	0.144, 0.216
[4-12)	362	136	6, (0.011)	0.309	0.268, 0.355
[12-26)	302	185	13, (0.023)	0.422	0.378, 0.470
[26-40)	247	210	16, (0.028)	0.481	0.435, 0.529
[40-52)	220	220	111, (0.194)	0.505	0.459, 0.553
[52-EoT]	138	220	288, (0.504)	0.505	0.459, 0.553
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	7.86	5.00, 10.43			
50th Percentile	47.71	31.29, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	433	91	3, (0.005)	0.211	0.175, 0.252
[4-12)	340	153	5, (0.009)	0.355	0.312, 0.402
[12-26)	276	200	10, (0.018)	0.465	0.419, 0.514
[26-40)	226	226	16, (0.028)	0.528	0.481, 0.576
[40-52)	194	237	92, (0.161)	0.555	0.508, 0.602
[52-EoT]	122	237	251, (0.440)	0.555	0.508, 0.602
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.29	3.86, 7.43			
50th Percentile	33.57	22.71, 48.29			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored
at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	213	43	2, (0.007)	0.202	0.154, 0.262
[4-12)	169	79	4, (0.014)	0.373	0.312, 0.442
[12-26)	131	98	8, (0.028)	0.465	0.401, 0.535
[26-40)	108	105	11, (0.038)	0.501	0.435, 0.570
[40-52)	99	114	53, (0.185)	0.547	0.480, 0.616
[52-EoT]	56	114	137, (0.477)	0.547	0.480, 0.616
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.86	3.29, 8.57			
50th Percentile	36.57	17.86, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Time to First Moderate Asthma Exacerbations stratified by Use of spacer - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium	3.00				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535	14.14				
pMDI HS					
CHF 5993 pMDI HS - CHF 1535	11.14				
pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15g Time to First Moderate Asthma Exacerbations by Use of spacer - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Use of spacer: Yes						
Number of Patients Included in Model	129	138	74			
Number of Censored Patients	66	55	38			
Treatment				0.141		
Country				0.003**		
Number of Asthma Exacerbations in Previous Year				0.160		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.737 [0.529, 1.027]	0.072
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.985 [0.651, 1.490]	0.941
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.748 [0.503, 1.114]	0.154

Produced: 17 December 2020 Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15g Time to First Moderate Asthma Exacerbations by Use of spacer - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Use of spacer: No						
Number of Patients Included in Model	442	433	213			
Number of Censored Patients	222	196	99			
Effect						
Treatment				0.168		
Country				<0.001***		
Number of Asthma Exacerbations in Previous Year				0.126		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.842 [0.701, 1.013]	0.068
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.870 [0.693, 1.091]	0.228
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.968 [0.774, 1.211]	0.779

Produced: 17 December 2020 Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12h Statistical Analysis of Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.200	
Country				0.043*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.146	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.673 [1.428, 1.961]	1.780 [1.526, 2.077]	1.376 [1.088, 1.742]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.940 [0.753, 1.173] 0.582
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.216 [0.914, 1.616] 0.179
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.773 [0.583, 1.025] 0.074

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12h Statistical Analysis of Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.593	
Country				0.003**	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.161	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.196 [0.987, 1.449]	1.372 [1.132, 1.663]	1.336 [1.022, 1.748]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.872 [0.664, 1.145] 0.324
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.895 [0.643, 1.247] 0.512
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.974 [0.700, 1.355] 0.876

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Relevant Concomitant Cardiovascular Diseases: Yes CHF 5993 pMDI HS (N=571)					
[0-4)	273	52	2, (0.004)	0.190	0.149, 0.242
[4-12)	221	93	6, (0.011)	0.342	0.289, 0.402
[12-26)	177	125	13, (0.023)	0.462	0.405, 0.523
[26-40)	142	147	16, (0.028)	0.546	0.488, 0.607
[40-52)	117	153	111, (0.194)	0.570	0.511, 0.630
[52-EoT]	69	153	288, (0.504)	0.570	0.511, 0.630
Percentile	Estimates (Weeks)		95% CI		
25th Percentile	7.00		4.14, 8.86		
50th Percentile	29.57		20.57, 45.29		
75th Percentile	NonEst		NonEst, NonEst		

Produced: 17 December 2020 Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	287	72	3, (0.005)	0.252	0.206, 0.306
[4-12)	213	116	5, (0.009)	0.406	0.352, 0.466
[12-26)	169	150	10, (0.018)	0.527	0.470, 0.586
[26-40)	132	163	16, (0.028)	0.574	0.517, 0.632
[40-52)	116	175	92, (0.161)	0.618	0.562, 0.675
[52-EoT]	76	175	251, (0.440)	0.618	0.562, 0.675
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	3.86	2.14, 5.71			
50th Percentile	20.14	15.14, 35.71			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	134	27	2, (0.007)	0.201	0.143, 0.280
[4-12)	107	50	4, (0.014)	0.373	0.297, 0.461
[12-26)	84	67	8, (0.028)	0.502	0.421, 0.590
[26-40)	65	74	11, (0.038)	0.557	0.474, 0.643
[40-52)	57	83	53, (0.185)	0.627	0.545, 0.709
[52-EoT]	33	83	137, (0.477)	0.627	0.545, 0.709
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.86	3.14, 9.43			
50th Percentile	25.57	13.00, 48.57			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments					
CHF 1535 pMDI HS + Tiotropium	Median difference 5.43				
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS	9.43				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium	4.00				

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Relevant Concomitant Cardiovascular Diseases: No CHF 5993 pMDI HS (N=571)					
[0-4)	298	44	2, (0.004)	0.148	0.112, 0.194
[4-12)	252	82	6, (0.011)	0.277	0.230, 0.332
[12-26)	213	109	13, (0.023)	0.370	0.317, 0.428
[26-40)	182	122	16, (0.028)	0.415	0.361, 0.473
[40-52)	169	130	111, (0.194)	0.443	0.388, 0.502
[52-EoT]	108	130	288, (0.504)	0.443	0.388, 0.502
Percentile	Estimates (Weeks)		95% CI		
25th Percentile	9.57		5.86, 14.14		
50th Percentile	NonEst		50.86, NonEst		
75th Percentile	NonEst		NonEst, NonEst		

Produced: 17 December 2020 Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	284	55	3, (0.005)	0.194	0.153, 0.245
[4-12)	228	90	5, (0.009)	0.318	0.267, 0.376
[12-26)	191	120	10, (0.018)	0.425	0.370, 0.485
[26-40)	159	139	16, (0.028)	0.495	0.438, 0.555
[40-52)	137	145	92, (0.161)	0.517	0.460, 0.577
[52-EoT]	83	145	251, (0.440)	0.517	0.460, 0.577
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	6.14	4.14, 10.71			
50th Percentile	45.00	30.00, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	153	31	2, (0.007)	0.203	0.148, 0.276
[4-12)	120	52	4, (0.014)	0.344	0.274, 0.426
[12-26)	97	60	8, (0.028)	0.398	0.325, 0.481
[26-40)	87	64	11, (0.038)	0.427	0.352, 0.510
[40-52)	81	67	53, (0.185)	0.448	0.372, 0.532
[52-EoT]	51	67	137, (0.477)	0.448	0.372, 0.532
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.86	3.29, 9.43			
50th Percentile	NonEst	34.86, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13h Time to First Moderate Asthma Exacerbations stratified by Relevant concomitant cardiovascular disease - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium					
- CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15h Time to First Moderate Asthma Exacerbations by Relevant concomitant cardiovascular disease - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Number of Censored Patients	120	112	51		
Treatment				0.401	
Country				0.117	
Number of Asthma Exacerbations in Previous Year				0.491	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.861 [0.692, 1.071] 0.179
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.907 [0.693, 1.187] 0.478
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.949 [0.729, 1.234] 0.695

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15h Time to First Moderate Asthma Exacerbations by Relevant concomitant cardiovascular disease - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Relevant Concomitant Cardiovascular Diseases: No						
Number of Patients Included in Model	298	284	153			
Number of Censored Patients	168	139	86			
Effect						
Treatment				0.085		
Country				<0.001***		
Number of Asthma Exacerbations in Previous Year				0.005**		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.765 [0.603, 0.971]	0.028*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.904 [0.672, 1.215]	0.503
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.846 [0.633, 1.132]	0.261

Produced: 17 December 2020 Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, country, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.12i Statistical Analysis of Moderate Asthma Exacerbations stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.077	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.678	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.654 [1.398, 1.956]	1.684 [1.424, 1.992]	1.213 [0.944, 1.558]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.982 [0.774, 1.246] 0.881
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.364 [1.009, 1.845] 0.044*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.720 [0.532, 0.974] 0.033*

Produced: 17 December 2020

Page 1 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.12i Statistical Analysis of Moderate Asthma Exacerbations stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.236	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.058	
Adjusted Exacerbation Rate per Patient per Year [95% CI]	1.268 [1.054, 1.526]	1.521 [1.270, 1.822]	1.609 [1.249, 2.073]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.834 [0.644, 1.079] 0.168
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.788 [0.576, 1.080] 0.138
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.058 [0.775, 1.444] 0.725

Produced: 17 December 2020

Page 2 of 2

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Region: Europe					
CHF 5993 pMDI HS (N=571)					
[0-4)	319	58	2, (0.004)	0.182	0.144, 0.229
[4-12)	260	98	6, (0.011)	0.309	0.261, 0.363
[12-26)	217	133	13, (0.023)	0.422	0.369, 0.478
[26-40)	178	152	16, (0.028)	0.484	0.430, 0.541
[40-52)	157	165	111, (0.194)	0.527	0.473, 0.583
[52-EoT]	92	165	288, (0.504)	0.527	0.473, 0.583
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	7.29	4.71, 10.71			
50th Percentile	46.57	30.29, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	319	70	3, (0.005)	0.220	0.178, 0.270
[4-12)	247	107	5, (0.009)	0.337	0.288, 0.392
[12-26)	209	143	10, (0.018)	0.452	0.399, 0.508
[26-40)	170	166	16, (0.028)	0.526	0.472, 0.583
[40-52)	144	177	92, (0.161)	0.563	0.509, 0.619
[52-EoT]	85	177	251, (0.440)	0.563	0.509, 0.619
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	5.43	3.43, 7.86			
50th Percentile	33.57	22.71, 50.43			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	160	26	2, (0.007)	0.162	0.114, 0.229
[4-12)	133	46	4, (0.014)	0.289	0.225, 0.367
[12-26)	112	60	8, (0.028)	0.379	0.308, 0.459
[26-40)	96	66	11, (0.038)	0.418	0.346, 0.500
[40-52)	88	70	53, (0.185)	0.445	0.371, 0.527
[52-EoT]	53	70	137, (0.477)	0.445	0.371, 0.527
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	8.57	4.86, 13.00			
50th Percentile	NonEst	44.57, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments	Median difference				
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS	13.00				
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 4 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Region: Rest of World CHF 5993 pMDI HS (N=571)					
[0-4)	252	38	2, (0.004)	0.151	0.112, 0.202
[4-12)	213	77	6, (0.011)	0.307	0.254, 0.368
[12-26)	173	101	13, (0.023)	0.404	0.346, 0.468
[26-40)	146	117	16, (0.028)	0.470	0.410, 0.534
[40-52)	129	118	111, (0.194)	0.474	0.414, 0.538
[52-EoT]	85	118	288, (0.504)	0.474	0.414, 0.538
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	8.43	5.86, 11.43			
50th Percentile	NonEst	28.71, NonEst			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS (N=571)					
[0-4)	252	57	3, (0.005)	0.227	0.180, 0.284
[4-12)	194	99	5, (0.009)	0.394	0.337, 0.458
[12-26)	151	127	10, (0.018)	0.508	0.448, 0.572
[26-40)	121	136	16, (0.028)	0.545	0.485, 0.608
[40-52)	109	143	92, (0.161)	0.574	0.514, 0.636
[52-EoT]	74	143	251, (0.440)	0.574	0.514, 0.636
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	4.29	2.86, 6.71			
50th Percentile	23.29	16.14, 47.00			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis
(Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
CHF 1535 pMDI HS + Tiotropium (N=287)					
[0-4)	127	32	2, (0.007)	0.253	0.186, 0.338
[4-12)	94	56	4, (0.014)	0.445	0.363, 0.536
[12-26)	69	67	8, (0.028)	0.534	0.450, 0.624
[26-40)	56	72	11, (0.038)	0.576	0.491, 0.664
[40-52)	50	80	53, (0.185)	0.644	0.560, 0.728
[52-EoT]	31	80	137, (0.477)	0.644	0.560, 0.728
Percentile	Estimates (Weeks)	95% CI			
25th Percentile	3.86	2.29, 6.29			
50th Percentile	17.43	9.86, 46.00			
75th Percentile	NonEst	NonEst, NonEst			

Produced: 17 December 2020 Page 7 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.13i Time to First Moderate Asthma Exacerbations stratified by Region - Kaplan-Meier Analysis (Intention-to-Treat Population)

Time (Weeks)	Number of Exacerbation* Free Patients at Beginning of Study Period	Cumulative Number of Patients with Exacerbation* at the End of the Period	Cumulative Number of Censored Patients at the End of the Period (%)	Probability of Having Experienced an Exacerbation* at the End of the Period	95% Confidence Interval
Treatments					
CHF 1535 pMDI HS + Tiotropium	Median difference				
- CHF 1535 pMDI HS	-5.86				
CHF 5993 pMDI HS - CHF 1535 pMDI HS					
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					

Produced: 17 December 2020 Page 8 of 8

Source: Listing 16.2.6.2.6

Notes: [1] * Moderate Asthma Exacerbations

[2] EoT = End of Treatment

[3] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15i Time to First Moderate Asthma Exacerbations by Region - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Region: Europe						
Number of Patients Included in Model	319	319	160			
Number of Censored Patients	154	142	90			
Treatment				0.072		
Number of Asthma Exacerbations in Previous Year				0.257		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.888 [0.718, 1.098]	0.271
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.225 [0.926, 1.621]	0.155
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.725 [0.549, 0.956]	0.023*

Produced: 17 December 2020 Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

Table 15.2.15i Time to First Moderate Asthma Exacerbations by Region - Cox Proportional Hazards Analysis (Intention-to-Treat Population)

Stratum	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Hazard Ratio [95% Wald CI]	p-value
Region: Rest of World						
Number of Patients Included in Model	252	252	127			
Number of Censored Patients	134	109	47			
Effect						
Treatment				0.002**		
Number of Asthma Exacerbations in Previous Year				0.049*		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.732 [0.574, 0.934]	0.012*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.619 [0.465, 0.824]	<0.001***
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.183 [0.899, 1.556]	0.231

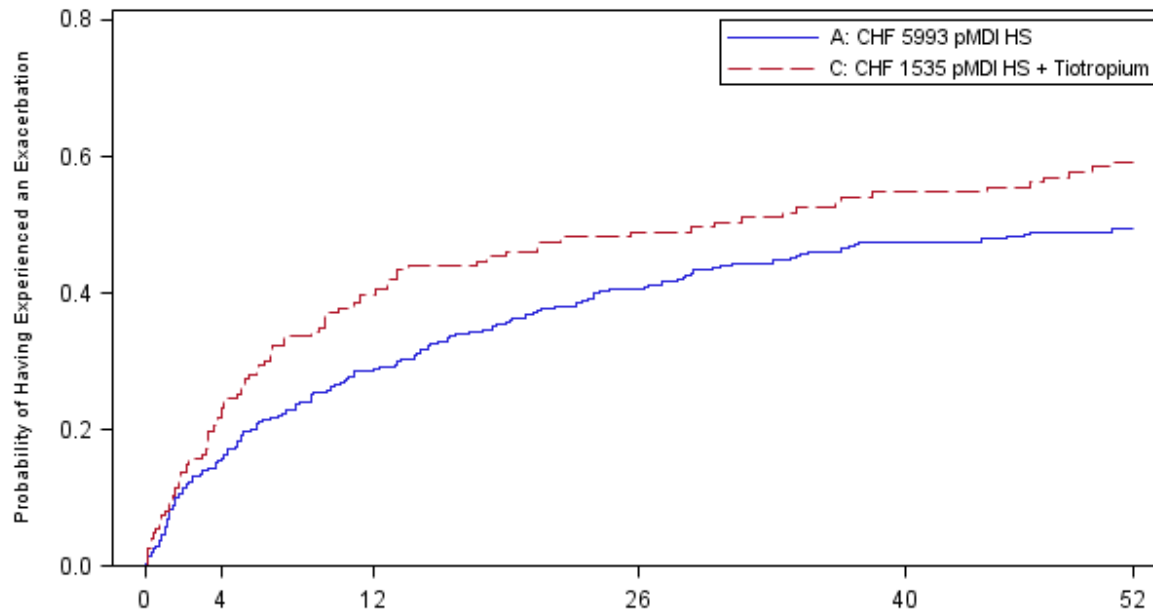
Produced: 17 December 2020 Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a Cox proportional hazards model including treatment, number of asthma exacerbations in the previous year as factors

[2] Patients who did not have a Moderate Asthma Exacerbations or discontinued before having one are censored at min(date of completion/discontinuation, date of Visit 7 or study termination visit)

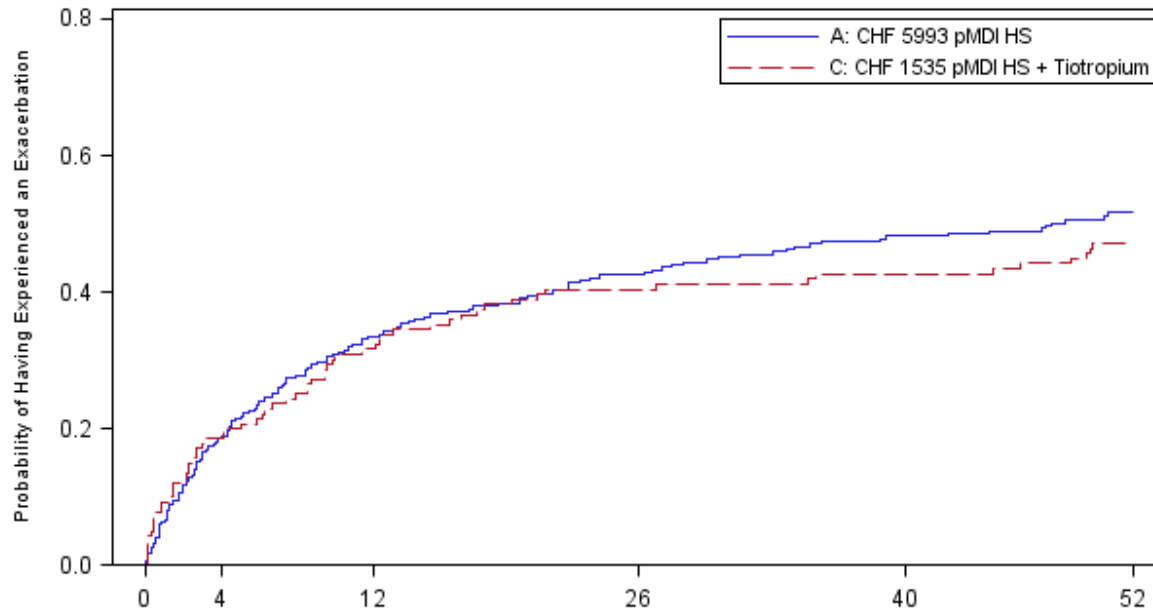
Figure 15.2.16f1 Time to Moderate Asthma Exacerbations Stratified by Degree of reversibility at screening -
 Kaplan Meier Analysis
 Degree of reversibility at screening: (200-400] mL
 (Intention-to-Treat Population)



Number of Patients at Risk

A:	299	253	211	171	149	87
C:	147	113	87	72	62	36
				Week		

Figure 15.2.16f2 Time to Moderate Asthma Exacerbations Stratified by Degree of reversibility at screening - Kaplan Meier Analysis
 Degree of reversibility at screening: > 400 mL
 (Intention-to-Treat Population)



Number of Patients at Risk

A:	271	219	178	152	136	89
C:	140	114	94	80	76	48
				Week		

ADDITIONAL_TLF_BATCH2_ASTHMA_SYMPTOMS

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch2

Date of Production: 17/12/2020

Identification Code: Additional_TLF_batch2_Asthma_Symptoms_CCD-05993AB2-02_20201217(Batch2)

Table 17.2.11a Statistical Analysis of Average Daily Asthma Symptoms score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.870
Inter-Visit Period			0.480
Treatment*Inter-Visit Period			0.256
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.491
Age Group Treatment Interaction			0.695

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11a Statistical Analysis of Average Daily Asthma Symptoms score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.258
Inter-Visit Period			0.499
Treatment*Inter-Visit Period			0.132
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.445
Age Group Treatment Interaction			0.420

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11a Statistical Analysis of Average Daily Asthma Symptoms score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.650
Inter-Visit Period			0.364
Treatment*Inter-Visit Period			0.580
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.784
Age Group Treatment Interaction			0.797

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11a Statistical Analysis of Average Daily Asthma Symptoms score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.736
Inter-Visit Period			0.234
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.383
Age Group Treatment Interaction			0.423

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11a Statistical Analysis of Average Daily Asthma Symptoms score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.765
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.622
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.733
Age Group Treatment Interaction			0.719

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11a Statistical Analysis of Average Daily Asthma Symptoms score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.443
Inter-Visit Period			0.171
Treatment*Inter-Visit Period			0.688
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.600
Age Group Treatment Interaction			0.336

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11b Statistical Analysis of Average Daily Asthma Symptoms score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.726
Inter-Visit Period			0.480
Treatment*Inter-Visit Period			0.257
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.487
Gender Treatment Interaction			0.317

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11b Statistical Analysis of Average Daily Asthma Symptoms score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.487
Inter-Visit Period			0.499
Treatment*Inter-Visit Period			0.132
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.451
Gender Treatment Interaction			0.758

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11b Statistical Analysis of Average Daily Asthma Symptoms score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.373
Inter-Visit Period			0.364
Treatment*Inter-Visit Period			0.580
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.159
Gender Treatment Interaction			0.625

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11b Statistical Analysis of Average Daily Asthma Symptoms score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.642
Inter-Visit Period			0.234
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.783
Gender Treatment Interaction			0.344

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11b Statistical Analysis of Average Daily Asthma Symptoms score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.669
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.623
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.910
Gender Treatment Interaction			0.160

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11b Statistical Analysis of Average Daily Asthma Symptoms score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.869
Inter-Visit Period			0.171
Treatment*Inter-Visit Period			0.689
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.944
Gender Treatment Interaction			0.832

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11c Statistical Analysis of Average Daily Asthma Symptoms score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.971
Inter-Visit Period			0.480
Treatment*Inter-Visit Period			0.258
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.053
BMI Class Treatment Interaction			0.746

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11c Statistical Analysis of Average Daily Asthma Symptoms score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.472
Inter-Visit Period			0.499
Treatment*Inter-Visit Period			0.134
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.204
BMI Class Treatment Interaction			0.931

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11c Statistical Analysis of Average Daily Asthma Symptoms score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.441
Inter-Visit Period			0.365
Treatment*Inter-Visit Period			0.583
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.014*
BMI Class Treatment Interaction			0.584

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11c Statistical Analysis of Average Daily Asthma Symptoms score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.978
Inter-Visit Period			0.234
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.447
BMI Class Treatment Interaction			0.349

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11c Statistical Analysis of Average Daily Asthma Symptoms score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.977
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.624
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.028*
BMI Class Treatment Interaction			0.842

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11c Statistical Analysis of Average Daily Asthma Symptoms score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.824
Inter-Visit Period			0.171
Treatment*Inter-Visit Period			0.691
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.097
BMI Class Treatment Interaction			0.959

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11d Statistical Analysis of Average Daily Asthma Symptoms score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.100
Inter-Visit Period			0.480
Treatment*Inter-Visit Period			0.257
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.822
Smoking Status Treatment Interaction			0.017*

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11d Statistical Analysis of Average Daily Asthma Symptoms score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.405
Inter-Visit Period			0.500
Treatment*Inter-Visit Period			0.133
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.813
Smoking Status Treatment Interaction			0.030*

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11d Statistical Analysis of Average Daily Asthma Symptoms score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.103
Inter-Visit Period			0.364
Treatment*Inter-Visit Period			0.581
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.511
Smoking Status Treatment Interaction			0.121

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11d Statistical Analysis of Average Daily Asthma Symptoms score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.152
Inter-Visit Period			0.233
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.601
Smoking Status Treatment Interaction			0.059

Produced: 17 December 2020

Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11d Statistical Analysis of Average Daily Asthma Symptoms score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.066
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.623
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.861
Smoking Status Treatment Interaction			0.007**

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11d Statistical Analysis of Average Daily Asthma Symptoms score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.247
Inter-Visit Period			0.171
Treatment*Inter-Visit Period			0.689
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.636
Smoking Status Treatment Interaction			0.045*

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11e Statistical Analysis of Average Daily Asthma Symptoms score including Number of Exacerbation in the Previous year
 - Interaction Test
 (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.255
Inter-Visit Period			0.479
Treatment*Inter-Visit Period			0.257
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.011*
Number of Exacerbation in the Previous year Treatment Interaction			0.059

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11e Statistical Analysis of Average Daily Asthma Symptoms score including Number of Exacerbation in the Previous year
 - Interaction Test
 (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.701
Inter-Visit Period			0.498
Treatment*Inter-Visit Period			0.133
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.009**
Number of Exacerbation in the Previous year Treatment Interaction			0.057

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11e Statistical Analysis of Average Daily Asthma Symptoms score including Number of Exacerbation in the Previous year
 - Interaction Test
 (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.111
Inter-Visit Period			0.365
Treatment*Inter-Visit Period			0.580
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.007**
Number of Exacerbation in the Previous year Treatment Interaction			0.110

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11e Statistical Analysis of Average Daily Asthma Symptoms score including Number of Exacerbation in the Previous year
 - Interaction Test
 (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.495
Inter-Visit Period			0.233
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.070
Number of Exacerbation in the Previous year Treatment Interaction			0.417

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11e Statistical Analysis of Average Daily Asthma Symptoms score including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.266
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.622
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.042*
Number of Exacerbation in the Previous year Treatment Interaction			0.055

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11e Statistical Analysis of Average Daily Asthma Symptoms score including Number of Exacerbation in the Previous year
 - Interaction Test
 (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.558
Inter-Visit Period			0.171
Treatment*Inter-Visit Period			0.689
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.006**
Number of Exacerbation in the Previous year Treatment Interaction			0.178

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11f Statistical Analysis of Average Daily Asthma Symptoms score including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.938
Inter-Visit Period			0.499
Treatment*Inter-Visit Period			0.238
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.127
Degree of reversibility at screening (delta FEV1)			0.660
Treatment Interaction			

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11f Statistical Analysis of Average Daily Asthma Symptoms score including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.413
Inter-Visit Period			0.506
Treatment*Inter-Visit Period			0.129
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.061
Degree of reversibility at screening (delta FEV1)			0.771
Treatment Interaction			

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11f Statistical Analysis of Average Daily Asthma Symptoms score including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.449
Inter-Visit Period			0.380
Treatment*Inter-Visit Period			0.563
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.635
Degree of reversibility at screening (delta FEV1)			0.297
Treatment Interaction			

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11f Statistical Analysis of Average Daily Asthma Symptoms score including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.849
Inter-Visit Period			0.257
Treatment*Inter-Visit Period			0.165
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.217
Degree of reversibility at screening (delta FEV1)			0.397
Treatment Interaction			

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11f Statistical Analysis of Average Daily Asthma Symptoms score including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.940
Inter-Visit Period			0.014*
Treatment*Inter-Visit Period			0.600
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.039*
Degree of reversibility at screening (delta FEV1)			0.895
Treatment Interaction			

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11f Statistical Analysis of Average Daily Asthma Symptoms score including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.783
Inter-Visit Period			0.173
Treatment*Inter-Visit Period			0.687
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.614
Degree of reversibility at screening (delta FEV1)			0.302
Treatment Interaction			

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11g Statistical Analysis of Average Daily Asthma Symptoms score including Use of Spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.929
Inter-Visit Period			0.479
Treatment*Inter-Visit Period			0.256
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.087
Use of Spacer Treatment Interaction			0.967

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11g Statistical Analysis of Average Daily Asthma Symptoms score including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.677
Inter-Visit Period			0.498
Treatment*Inter-Visit Period			0.132
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.048*
Use of Spacer Treatment Interaction			0.465

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11g Statistical Analysis of Average Daily Asthma Symptoms score including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.453
Inter-Visit Period			0.363
Treatment*Inter-Visit Period			0.579
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.210
Use of Spacer Treatment Interaction			0.902

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11g Statistical Analysis of Average Daily Asthma Symptoms score including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.750
Inter-Visit Period			0.234
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.199
Use of Spacer Treatment Interaction			0.781

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11g Statistical Analysis of Average Daily Asthma Symptoms score including Use of Spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.799
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.622
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.168
Use of Spacer Treatment Interaction			0.486

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11g Statistical Analysis of Average Daily Asthma Symptoms score including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.978
Inter-Visit Period			0.170
Treatment*Inter-Visit Period			0.688
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.120
Use of Spacer Treatment Interaction			0.565

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11h Statistical Analysis of Average Daily Asthma Symptoms score including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.910
Inter-Visit Period			0.480
Treatment*Inter-Visit Period			0.257
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.542
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.807

Produced: 17 December 2020 Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11h Statistical Analysis of Average Daily Asthma Symptoms score including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.409
Inter-Visit Period			0.500
Treatment*Inter-Visit Period			0.134
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.167
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.506

Produced: 17 December 2020 Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11h Statistical Analysis of Average Daily Asthma Symptoms score including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.422
Inter-Visit Period			0.364
Treatment*Inter-Visit Period			0.580
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.536
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.901

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11h Statistical Analysis of Average Daily Asthma Symptoms score including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.801
Inter-Visit Period			0.234
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.989
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.985

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11h Statistical Analysis of Average Daily Asthma Symptoms score including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.920
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.622
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.899
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.886

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11h Statistical Analysis of Average Daily Asthma Symptoms score including Relevant Concomitant Cardiovascular Diseases
 - Interaction Test
 (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.821
Inter-Visit Period			0.171
Treatment*Inter-Visit Period			0.688
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.868
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.871

Produced: 17 December 2020

Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11i Statistical Analysis of Average Daily Asthma Symptoms score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Total Daily Asthma Symptoms Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.955
Inter-Visit Period			0.480
Treatment*Inter-Visit Period			0.257
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.331
Region Treatment Interaction			0.459

Produced: 17 December 2020

Page 1 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11i Statistical Analysis of Average Daily Asthma Symptoms score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Cough			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.373
Inter-Visit Period			0.499
Treatment*Inter-Visit Period			0.133
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.845
Region Treatment Interaction			0.268

Produced: 17 December 2020

Page 2 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11i Statistical Analysis of Average Daily Asthma Symptoms score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Athma Symptom Score: Wheeze			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.427
Inter-Visit Period			0.365
Treatment*Inter-Visit Period			0.580
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.316
Region Treatment Interaction			0.863

Produced: 17 December 2020 Page 3 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11i Statistical Analysis of Average Daily Asthma Symptoms score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Chest Tightness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.838
Inter-Visit Period			0.234
Treatment*Inter-Visit Period			0.187
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.270
Region Treatment Interaction			0.641

Produced: 17 December 2020 Page 4 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11i Statistical Analysis of Average Daily Asthma Symptoms score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Daily Asthma Symptom Score: Breathlessness			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.968
Inter-Visit Period			0.013*
Treatment*Inter-Visit Period			0.623
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.271
Region Treatment Interaction			0.496

Produced: 17 December 2020 Page 5 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.11i Statistical Analysis of Average Daily Asthma Symptoms score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
Average Overall Daily Asthma Symptom Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.749
Inter-Visit Period			0.171
Treatment*Inter-Visit Period			0.689
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.238
Region Treatment Interaction			0.337

Produced: 17 December 2020 Page 6 of 6

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: <65 years old					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	473	446	246		
Effect					
Treatment				0.701	
Inter-Visit Period				0.037*	
Treatment*Inter-Visit Period				0.645	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.122	-0.122	-0.143		
[95% CI]	[-0.147, -0.098]	[-0.147, -0.097]	[-0.177, -0.110]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.035, 0.034] 0.968
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.020, 0.062] 0.316
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.064, 0.020] 0.305

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.175	-0.174	-0.196		
[95% CI]	[-0.205, -0.146]	[-0.204, -0.143]	[-0.236, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.044, 0.040] 0.928
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.030, 0.070] 0.435
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.073, 0.029] 0.397
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.211	-0.203	-0.226		
[95% CI]	[-0.244, -0.178]	[-0.236, -0.169]	[-0.271, -0.180]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.055, 0.039] 0.729
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.041, 0.071] 0.608
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.079, 0.034] 0.427

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.229	-0.209	-0.237		
[95% CI]	[-0.265, -0.193]	[-0.246, -0.173]	[-0.287, -0.187]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.071, 0.032] 0.448
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.054, 0.069] 0.808
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.089, 0.034] 0.384
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.235	-0.206	-0.216		
[95% CI]	[-0.273, -0.197]	[-0.245, -0.167]	[-0.268, -0.163]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.083, 0.025] 0.295
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.019 [-0.084, 0.046] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.075, 0.056] 0.769

Produced: 17 December 2020

Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.186	-0.181	-0.204		
[95% CI]	[-0.215, -0.158]	[-0.211, -0.152]	[-0.244, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.047, 0.036] 0.806
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.032, 0.067] 0.491
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.072, 0.027] 0.376
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.209	-0.194	-0.215		
[95% CI]	[-0.240, -0.178]	[-0.227, -0.162]	[-0.259, -0.172]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.060, 0.030] 0.524
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.047, 0.060] 0.819
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.075, 0.033] 0.450

Produced: 17 December 2020

Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	473	446	246		
Effect					
Treatment				0.827	
Inter-Visit Period				0.038*	
Treatment*Inter-Visit Period				0.256	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.136	-0.141	-0.139		
[95% CI]	[-0.164, -0.108]	[-0.169, -0.112]	[-0.178, -0.101]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.035, 0.044] 0.819
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.044, 0.051] 0.891
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.047, 0.049] 0.957

Produced: 17 December 2020 Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.196	-0.202	-0.200		
[95% CI]	[-0.230, -0.162]	[-0.237, -0.167]	[-0.248, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.042, 0.056] 0.790
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.054, 0.063] 0.879
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.057, 0.061] 0.944
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.244	-0.236	-0.245		
[95% CI]	[-0.281, -0.207]	[-0.274, -0.197]	[-0.296, -0.193]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.062, 0.045] 0.750
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.063, 0.064] 0.988
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.073, 0.055] 0.780

Produced: 17 December 2020 Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.266	-0.238	-0.262		
[95% CI]	[-0.306, -0.226]	[-0.279, -0.197]	[-0.318, -0.207]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.028 [-0.085, 0.029] 0.331
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.072, 0.065] 0.917
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.094, 0.044] 0.481
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.276	-0.230	-0.231		
[95% CI]	[-0.318, -0.234]	[-0.273, -0.187]	[-0.289, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.046 [-0.106, 0.014] 0.130
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.045 [-0.116, 0.027] 0.219
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.074, 0.071] 0.969

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.213	-0.211	-0.215		
[95% CI]	[-0.245, -0.180]	[-0.244, -0.177]	[-0.260, -0.170]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.048, 0.044] 0.936
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.053, 0.057] 0.939
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.060, 0.052] 0.886
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.242	-0.222	-0.231		
[95% CI]	[-0.276, -0.207]	[-0.258, -0.187]	[-0.279, -0.183]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.069, 0.030] 0.446
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.069, 0.049] 0.734
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.069, 0.051] 0.767

Produced: 17 December 2020 Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	473	446	246		
Effect					
Treatment				0.665	
Inter-Visit Period				0.055	
Treatment*Inter-Visit Period				0.572	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.138	-0.135	-0.171		
[95% CI]	[-0.166, -0.111]	[-0.163, -0.106]	[-0.209, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.043, 0.036] 0.859
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.032 [-0.015, 0.080] 0.179
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.084, 0.012] 0.139

Produced: 17 December 2020 Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.194	-0.202	-0.222		
[95% CI]	[-0.228, -0.161]	[-0.236, -0.167]	[-0.268, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.041, 0.055] 0.771
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.030, 0.084] 0.355
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.078, 0.038] 0.501
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.220	-0.225	-0.243		
[95% CI]	[-0.257, -0.183]	[-0.263, -0.187]	[-0.294, -0.192]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.048, 0.058] 0.847
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.040, 0.086] 0.466
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.082, 0.045] 0.574

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.240	-0.224	-0.259		
[95% CI]	[-0.280, -0.200]	[-0.265, -0.183]	[-0.314, -0.203]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.073, 0.042] 0.590
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.049, 0.088] 0.581
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.104, 0.034] 0.320
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.244	-0.220	-0.239		
[95% CI]	[-0.286, -0.203]	[-0.263, -0.177]	[-0.297, -0.180]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.084, 0.036] 0.429
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.078, 0.066] 0.873
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.091, 0.054] 0.619

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.199	-0.204	-0.225		
[95% CI]	[-0.232, -0.167]	[-0.237, -0.171]	[-0.270, -0.180]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.042, 0.051] 0.851
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.026 [-0.029, 0.081] 0.358
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.077, 0.034] 0.451
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.221	-0.213	-0.237		
[95% CI]	[-0.256, -0.186]	[-0.249, -0.177]	[-0.286, -0.189]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.058, 0.042] 0.765
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.043, 0.076] 0.581
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.085, 0.036] 0.427

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	473	446	246		
Effect					
Treatment				0.769	
Inter-Visit Period				0.013*	
Treatment*Inter-Visit Period				0.628	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.089	-0.095	-0.123		
[95% CI]	[-0.117, -0.061]	[-0.124, -0.067]	[-0.161, -0.084]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.034, 0.046] 0.763
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.034 [-0.014, 0.081] 0.169
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.076, 0.021] 0.266

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.131	-0.129	-0.163		
[95% CI]	[-0.164, -0.099]	[-0.162, -0.095]	[-0.208, -0.118]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.049, 0.044] 0.906
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.024, 0.087] 0.270
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.034 [-0.090, 0.022] 0.234
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.162	-0.164	-0.185		
[95% CI]	[-0.198, -0.126]	[-0.201, -0.128]	[-0.234, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.049, 0.054] 0.920
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.039, 0.084] 0.467
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.082, 0.042] 0.524

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.172	-0.179	-0.191		
[95% CI]	[-0.211, -0.132]	[-0.219, -0.138]	[-0.246, -0.136]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.050, 0.063] 0.813
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.048, 0.087] 0.574
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.081, 0.056] 0.718
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.178	-0.177	-0.169		
[95% CI]	[-0.219, -0.137]	[-0.219, -0.135]	[-0.226, -0.112]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.060, 0.058] 0.973
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.080, 0.061] 0.795
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.063, 0.079] 0.818

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.141	-0.143	-0.168		
[95% CI]	[-0.173, -0.110]	[-0.175, -0.110]	[-0.212, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.044, 0.047] 0.948
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.027, 0.081] 0.328
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.080, 0.029] 0.361
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.158	-0.160	-0.175		
[95% CI]	[-0.192, -0.124]	[-0.196, -0.125]	[-0.222, -0.127]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.047, 0.052] 0.925
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.042, 0.075] 0.581
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.074, 0.045] 0.639

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	473	446	246		
Effect					
Treatment				0.302	
Inter-Visit Period				0.002**	
Treatment*Inter-Visit Period				0.856	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.126	-0.115	-0.142		
[95% CI]	[-0.153, -0.098]	[-0.144, -0.086]	[-0.180, -0.103]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.051, 0.029] 0.600
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.032, 0.064] 0.507
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.075, 0.021] 0.274

Produced: 17 December 2020 Page 17 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.180	-0.160	-0.198		
[95% CI]	[-0.214, -0.147]	[-0.195, -0.125]	[-0.244, -0.151]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.069, 0.028] 0.405
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.040, 0.075] 0.549
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.096, 0.020] 0.199
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.219	-0.184	-0.231		
[95% CI]	[-0.256, -0.182]	[-0.222, -0.146]	[-0.282, -0.179]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.089, 0.018] 0.192
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.052, 0.075] 0.722
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.111, 0.017] 0.151

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.242	-0.196	-0.237		
[95% CI]	[-0.283, -0.202]	[-0.238, -0.154]	[-0.293, -0.181]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.046 [-0.104, 0.012] 0.119
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.074, 0.064] 0.886
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.041 [-0.111, 0.029] 0.249
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.244	-0.195	-0.226		
[95% CI]	[-0.287, -0.201]	[-0.239, -0.151]	[-0.285, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.049 [-0.110, 0.012] 0.115
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.091, 0.055] 0.634
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.105, 0.042] 0.403

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.193	-0.166	-0.207		
[95% CI]	[-0.226, -0.160]	[-0.200, -0.132]	[-0.252, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.074, 0.020] 0.259
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.042, 0.070] 0.621
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.041 [-0.098, 0.015] 0.154
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.218	-0.181	-0.220		
[95% CI]	[-0.253, -0.183]	[-0.217, -0.144]	[-0.269, -0.170]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.088, 0.014] 0.150
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.059, 0.062] 0.959
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.100, 0.022] 0.213

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	473	445	246		
Effect					
Treatment				0.545	
Inter-Visit Period				0.011*	
Treatment*Inter-Visit Period				0.961	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.131	-0.114	-0.138		
[95% CI]	[-0.160, -0.102]	[-0.144, -0.084]	[-0.179, -0.098]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.059, 0.025] 0.421
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.042, 0.057] 0.779
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.074, 0.026] 0.343

Produced: 17 December 2020 Page 21 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.196	-0.178	-0.202		
[95% CI]	[-0.230, -0.161]	[-0.214, -0.143]	[-0.250, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.067, 0.033] 0.502
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.053, 0.066] 0.840
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.084, 0.037] 0.449
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.228	-0.209	-0.238		
[95% CI]	[-0.265, -0.190]	[-0.247, -0.170]	[-0.291, -0.186]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.073, 0.035] 0.489
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.054, 0.075] 0.747
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.095, 0.035] 0.371

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.251	-0.221	-0.246		
[95% CI]	[-0.292, -0.210]	[-0.263, -0.179]	[-0.303, -0.189]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.030 [-0.089, 0.029] 0.311
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.076, 0.065] 0.873
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.096, 0.046] 0.495
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.255	-0.215	-0.237		
[95% CI]	[-0.298, -0.213]	[-0.259, -0.172]	[-0.297, -0.178]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.101, 0.021] 0.203
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.091, 0.055] 0.635
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.096, 0.052] 0.559

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.203	-0.185	-0.212		
[95% CI]	[-0.237, -0.169]	[-0.219, -0.150]	[-0.258, -0.165]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.066, 0.030] 0.459
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.049, 0.066] 0.766
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.085, 0.031] 0.363
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.228	-0.202	-0.227		
[95% CI]	[-0.264, -0.192]	[-0.239, -0.165]	[-0.277, -0.177]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.078, 0.025] 0.314
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.063, 0.060] 0.968
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.087, 0.037] 0.426

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.764	
Inter-Visit Period				0.029*	
Treatment*Inter-Visit Period				0.647	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.104	-0.112	-0.108		
[95% CI]	[-0.155, -0.054]	[-0.157, -0.066]	[-0.186, -0.030]		
p-value	<0.001***	<0.001***	0.007**		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.061, 0.075] 0.834
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.090, 0.097] 0.939
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.087, 0.094] 0.938

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.170	-0.150	-0.111		
[95% CI]	[-0.231, -0.109]	[-0.205, -0.095]	[-0.206, -0.016]		
p-value	<0.001***	<0.001***	0.023*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.103, 0.062] 0.628
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.059 [-0.172, 0.054] 0.307
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.039 [-0.072, 0.149] 0.491
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.207	-0.166	-0.164		
[95% CI]	[-0.277, -0.137]	[-0.229, -0.103]	[-0.273, -0.056]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.135, 0.053] 0.393
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.042 [-0.172, 0.087] 0.518
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.124, 0.127] 0.979

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.216	-0.197	-0.171		
[95% CI]	[-0.289, -0.143]	[-0.262, -0.132]	[-0.285, -0.058]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.117, 0.079] 0.701
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.045 [-0.180, 0.090] 0.513
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.026 [-0.106, 0.157] 0.700
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.234	-0.205	-0.183		
[95% CI]	[-0.306, -0.161]	[-0.270, -0.139]	[-0.297, -0.069]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.127, 0.069] 0.559
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.051 [-0.186, 0.085] 0.462
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.021 [-0.110, 0.153] 0.749

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.180	-0.153	-0.139		
[95% CI]	[-0.240, -0.119]	[-0.207, -0.098]	[-0.234, -0.045]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.109, 0.054] 0.513
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.040 [-0.152, 0.072] 0.478
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.013 [-0.096, 0.122] 0.810
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.202	-0.177	-0.158		
[95% CI]	[-0.266, -0.138]	[-0.234, -0.119]	[-0.258, -0.059]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.111, 0.060] 0.560
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.044 [-0.162, 0.074] 0.465
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.019 [-0.096, 0.133] 0.751

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.328	
Inter-Visit Period				0.384	
Treatment*Inter-Visit Period				0.586	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.116	-0.131	-0.075		
[95% CI]	[-0.178, -0.055]	[-0.186, -0.076]	[-0.170, 0.020]		
p-value	<0.001***	<0.001***	0.123		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.068, 0.096] 0.732
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.042 [-0.155, 0.071] 0.467
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.056 [-0.054, 0.166] 0.315

Produced: 17 December 2020 Page 29 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.206	-0.192	-0.110		
[95% CI]	[-0.278, -0.134]	[-0.257, -0.128]	[-0.222, 0.002]		
p-value	<0.001***	<0.001***	0.055		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.110, 0.083] 0.777
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.096 [-0.230, 0.037] 0.156
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.082 [-0.047, 0.212] 0.211
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.270	-0.221	-0.181		
[95% CI]	[-0.350, -0.190]	[-0.294, -0.149]	[-0.307, -0.055]		
p-value	<0.001***	<0.001***	0.005**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.049 [-0.157, 0.059] 0.374
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.089 [-0.238, 0.060] 0.242
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.040 [-0.105, 0.185] 0.587

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.287	-0.275	-0.180		
[95% CI]	[-0.370, -0.204]	[-0.350, -0.200]	[-0.311, -0.050]		
p-value	<0.001***	<0.001***	0.007**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.124, 0.099] 0.828
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.107 [-0.262, 0.048] 0.174
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.095 [-0.056, 0.245] 0.217
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.317	-0.276	-0.192		
[95% CI]	[-0.400, -0.234]	[-0.352, -0.200]	[-0.324, -0.060]		
p-value	<0.001***	<0.001***	0.005**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.154, 0.071] 0.470
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.126 [-0.282, 0.030] 0.114
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.084 [-0.068, 0.237] 0.276

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.227	-0.198	-0.143		
[95% CI]	[-0.295, -0.158]	[-0.260, -0.137]	[-0.250, -0.036]		
p-value	<0.001***	<0.001***	0.009**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.028 [-0.120, 0.064] 0.544
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.084 [-0.211, 0.043] 0.194
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.056 [-0.068, 0.179] 0.376
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.264	-0.237	-0.164		
[95% CI]	[-0.334, -0.194]	[-0.300, -0.174]	[-0.274, -0.054]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.122, 0.067] 0.574
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.100 [-0.231, 0.031] 0.134
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.073 [-0.054, 0.200] 0.261

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.907	
Inter-Visit Period				0.286	
Treatment*Inter-Visit Period				0.936	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.123	-0.138	-0.135		
[95% CI]	[-0.180, -0.066]	[-0.189, -0.086]	[-0.224, -0.046]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					0.015 [-0.062, 0.092] 0.705
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.094, 0.118] 0.820
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.100, 0.105] 0.960

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.172	-0.163	-0.167		
[95% CI]	[-0.238, -0.106]	[-0.222, -0.104]	[-0.269, -0.064]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.097, 0.079] 0.843
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.127, 0.116] 0.928
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.121, 0.115] 0.956
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.209	-0.202	-0.231		
[95% CI]	[-0.282, -0.136]	[-0.267, -0.136]	[-0.345, -0.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.105, 0.091] 0.886
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.113, 0.157] 0.747
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.029 [-0.161, 0.102] 0.661

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.204	-0.230	-0.256		
[95% CI]	[-0.282, -0.125]	[-0.301, -0.159]	[-0.379, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.026 [-0.080, 0.132] 0.627
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.052 [-0.094, 0.199] 0.483
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.169, 0.117] 0.720
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.216	-0.237	-0.265		
[95% CI]	[-0.295, -0.138]	[-0.309, -0.166]	[-0.389, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.021 [-0.085, 0.127] 0.700
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.049 [-0.098, 0.196] 0.513
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.171, 0.115] 0.700

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.184	-0.180	-0.196		
[95% CI]	[-0.248, -0.121]	[-0.237, -0.123]	[-0.295, -0.098]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.089, 0.081] 0.921
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.105, 0.129] 0.839
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.130, 0.098] 0.777
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.197	-0.207	-0.228		
[95% CI]	[-0.264, -0.129]	[-0.267, -0.146]	[-0.334, -0.123]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.081, 0.101] 0.833
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.094, 0.156] 0.621
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.143, 0.100] 0.726

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.438	
Inter-Visit Period				0.108	
Treatment*Inter-Visit Period				0.584	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.080	-0.075	-0.076		
[95% CI]	[-0.137, -0.023]	[-0.126, -0.024]	[-0.164, 0.012]		
p-value	0.006**	0.004**	0.091		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.082, 0.071] 0.891
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.109, 0.101] 0.937
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.103, 0.101] 0.983

Produced: 17 December 2020 Page 37 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.152	-0.094	-0.050		
[95% CI]	[-0.223, -0.082]	[-0.157, -0.031]	[-0.159, 0.059]		
p-value	<0.001***	0.004**	0.365		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.153, 0.036] 0.223
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.102 [-0.232, 0.027] 0.122
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.044 [-0.082, 0.170] 0.495
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.162	-0.099	-0.075		
[95% CI]	[-0.245, -0.080]	[-0.174, -0.025]	[-0.203, 0.054]		
p-value	<0.001***	0.009**	0.254		
CHF 5993 pMDI - CHF 1535 pMDI					-0.063 [-0.174, 0.048] 0.265
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.088 [-0.241, 0.065] 0.259
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.124, 0.173] 0.743

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.172	-0.120	-0.081		
[95% CI]	[-0.258, -0.085]	[-0.198, -0.042]	[-0.216, 0.054]		
p-value	<0.001***	0.003**	0.240		
CHF 5993 pMDI - CHF 1535 pMDI					-0.052 [-0.168, 0.064] 0.380
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.091 [-0.252, 0.070] 0.266
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.039 [-0.117, 0.195] 0.624
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.171	-0.129	-0.070		
[95% CI]	[-0.259, -0.083]	[-0.208, -0.049]	[-0.208, 0.069]		
p-value	<0.001***	0.002**	0.322		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.161, 0.076] 0.483
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.101 [-0.265, 0.063] 0.225
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.059 [-0.101, 0.219] 0.467

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.147	-0.094	-0.067		
[95% CI]	[-0.217, -0.077]	[-0.157, -0.031]	[-0.176, 0.042]		
p-value	<0.001***	0.004**	0.225		
CHF 5993 pMDI - CHF 1535 pMDI					-0.053 [-0.147, 0.042] 0.271
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.079 [-0.209, 0.050] 0.229
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.027 [-0.099, 0.153] 0.678
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.159	-0.109	-0.072		
[95% CI]	[-0.235, -0.083]	[-0.177, -0.041]	[-0.189, 0.046]		
p-value	<0.001***	0.002**	0.233		
CHF 5993 pMDI - CHF 1535 pMDI					-0.050 [-0.152, 0.052] 0.333
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.088 [-0.228, 0.053] 0.219
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.037 [-0.099, 0.173] 0.589

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.865	
Inter-Visit Period				0.001**	
Treatment*Inter-Visit Period				0.441	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.098	-0.104	-0.142		
[95% CI]	[-0.157, -0.038]	[-0.157, -0.050]	[-0.234, -0.050]		
p-value	0.001**	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.074, 0.086] 0.884
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.044 [-0.066, 0.153] 0.432
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.144, 0.068] 0.484

Produced: 17 December 2020 Page 41 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.150	-0.149	-0.113		
[95% CI]	[-0.226, -0.075]	[-0.217, -0.081]	[-0.230, 0.004]		
p-value	<0.001***	<0.001***	0.059		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.103, 0.100] 0.980
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.038 [-0.177, 0.102] 0.594
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.036 [-0.099, 0.172] 0.596
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.188	-0.143	-0.166		
[95% CI]	[-0.275, -0.102]	[-0.221, -0.065]	[-0.301, -0.031]		
p-value	<0.001***	<0.001***	0.016*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.162, 0.071] 0.442
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.183, 0.138] 0.782
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.179, 0.133] 0.772

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.204	-0.165	-0.170		
[95% CI]	[-0.295, -0.113]	[-0.248, -0.083]	[-0.313, -0.027]		
p-value	<0.001***	<0.001***	0.020*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.161, 0.084] 0.537
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.034 [-0.204, 0.136] 0.693
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.170, 0.161] 0.957
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.233	-0.179	-0.205		
[95% CI]	[-0.324, -0.142]	[-0.261, -0.097]	[-0.348, -0.062]		
p-value	<0.001***	<0.001***	0.005**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.054 [-0.176, 0.068] 0.386
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.197, 0.141] 0.744
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.191, 0.139] 0.758

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.163	-0.139	-0.146		
[95% CI]	[-0.237, -0.088]	[-0.205, -0.072]	[-0.261, -0.030]		
p-value	<0.001***	<0.001***	0.014*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.124, 0.076] 0.637
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.017 [-0.154, 0.120] 0.807
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.140, 0.126] 0.918
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.190	-0.155	-0.166		
[95% CI]	[-0.269, -0.111]	[-0.226, -0.084]	[-0.288, -0.043]		
p-value	<0.001***	<0.001***	0.008**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.141, 0.071] 0.517
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.170, 0.121] 0.744
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.152, 0.131] 0.882

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.693	
Inter-Visit Period				0.210	
Treatment*Inter-Visit Period				0.240	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.173	-0.116	-0.118		
[95% CI]	[-0.236, -0.110]	[-0.173, -0.060]	[-0.215, -0.020]		
p-value	<0.001***	<0.001***	0.019*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.142, 0.028] 0.189
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.056 [-0.172, 0.061] 0.347
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.114, 0.112] 0.985

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.248	-0.159	-0.169		
[95% CI]	[-0.321, -0.175]	[-0.225, -0.093]	[-0.284, -0.055]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.089 [-0.188, 0.010] 0.077
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.079 [-0.214, 0.057] 0.254
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.142, 0.122] 0.877
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.273	-0.223	-0.235		
[95% CI]	[-0.356, -0.190]	[-0.298, -0.149]	[-0.364, -0.106]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.050 [-0.161, 0.062] 0.382
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.038 [-0.191, 0.115] 0.626
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.161, 0.138] 0.879

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.243	-0.263	-0.251		
[95% CI]	[-0.331, -0.156]	[-0.342, -0.183]	[-0.389, -0.113]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.099, 0.138] 0.752
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.156, 0.171] 0.927
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.148, 0.171] 0.888
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.263	-0.242	-0.233		
[95% CI]	[-0.351, -0.174]	[-0.323, -0.162]	[-0.373, -0.094]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.140, 0.099] 0.739
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.029 [-0.195, 0.136] 0.726
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.152, 0.171] 0.911

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12a Statistical Analysis of Average Daily Asthma Symptoms score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.250	-0.187	-0.197		
[95% CI]	[-0.322, -0.178]	[-0.252, -0.123]	[-0.308, -0.085]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.063 [-0.159, 0.034] 0.202
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.053 [-0.186, 0.079] 0.430
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.139, 0.120] 0.884
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.251	-0.220	-0.220		
[95% CI]	[-0.327, -0.175]	[-0.289, -0.151]	[-0.339, -0.101]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.134, 0.072] 0.553
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.031 [-0.172, 0.110] 0.662
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.000 [-0.137, 0.138] 0.996

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.849	
Inter-Visit Period				0.123	
Treatment*Inter-Visit Period				0.113	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.098	-0.121	-0.149		
[95% CI]	[-0.134, -0.063]	[-0.154, -0.087]	[-0.200, -0.098]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.022 [-0.027, 0.071] 0.371
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.051 [-0.012, 0.113] 0.113
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.090, 0.033] 0.365

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.174	-0.172	-0.185		
[95% CI]	[-0.215, -0.133]	[-0.211, -0.133]	[-0.244, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.059, 0.055] 0.941
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.062, 0.083] 0.773
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.084, 0.058] 0.724
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.208	-0.199	-0.200		
[95% CI]	[-0.255, -0.161]	[-0.242, -0.155]	[-0.267, -0.133]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.073, 0.055] 0.776
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.090, 0.074] 0.846
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.081, 0.079] 0.977

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.240	-0.203	-0.206		
[95% CI]	[-0.291, -0.190]	[-0.250, -0.156]	[-0.279, -0.133]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.107, 0.032] 0.291
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.034 [-0.123, 0.054] 0.447
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.090, 0.084] 0.947
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.255	-0.200	-0.176		
[95% CI]	[-0.310, -0.199]	[-0.252, -0.148]	[-0.256, -0.096]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.131, 0.021] 0.157
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.079 [-0.176, 0.019] 0.114
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.072, 0.119] 0.627

Produced: 17 December 2020

Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.181	-0.178	-0.187		
[95% CI]	[-0.222, -0.140]	[-0.217, -0.140]	[-0.246, -0.129]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.058, 0.054] 0.938
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.065, 0.078] 0.854
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.079, 0.061] 0.803
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.214	-0.190	-0.190		
[95% CI]	[-0.258, -0.169]	[-0.232, -0.148]	[-0.254, -0.126]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.085, 0.037] 0.443
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.102, 0.054] 0.545
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.000 [-0.076, 0.077] 0.996

Produced: 17 December 2020

Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.588	
Inter-Visit Period				0.492	
Treatment*Inter-Visit Period				0.326	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.116	-0.135	-0.136		
[95% CI]	[-0.158, -0.075]	[-0.174, -0.097]	[-0.195, -0.076]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.037, 0.076] 0.505
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.053, 0.092] 0.599
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.000 [-0.071, 0.071] 0.996

Produced: 17 December 2020 Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.197	-0.203	-0.178		
[95% CI]	[-0.246, -0.148]	[-0.249, -0.158]	[-0.249, -0.108]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.061, 0.073] 0.861
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.019 [-0.105, 0.067] 0.663
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.059, 0.109] 0.559
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.244	-0.228	-0.207		
[95% CI]	[-0.298, -0.189]	[-0.279, -0.177]	[-0.285, -0.128]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.090, 0.059] 0.684
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.037 [-0.133, 0.059] 0.450
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.021 [-0.073, 0.115] 0.657

Produced: 17 December 2020

Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.287	-0.239	-0.228		
[95% CI]	[-0.344, -0.229]	[-0.293, -0.185]	[-0.311, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.048 [-0.127, 0.031] 0.237
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.059 [-0.160, 0.042] 0.254
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.088, 0.110] 0.824
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.311	-0.233	-0.210		
[95% CI]	[-0.373, -0.249]	[-0.291, -0.175]	[-0.300, -0.120]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.078 [-0.163, 0.007] 0.073
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.101 [-0.210, 0.008] 0.070
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.023 [-0.084, 0.130] 0.674

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.210	-0.206	-0.187		
[95% CI]	[-0.256, -0.163]	[-0.250, -0.163]	[-0.254, -0.120]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.067, 0.060] 0.913
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.104, 0.059] 0.585
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.019 [-0.061, 0.099] 0.639
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.254	-0.221	-0.203		
[95% CI]	[-0.303, -0.205]	[-0.267, -0.175]	[-0.274, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.100, 0.035] 0.344
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.050 [-0.137, 0.036] 0.252
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.018 [-0.067, 0.103] 0.679

Produced: 17 December 2020 Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.988	
Inter-Visit Period				0.040*	
Treatment*Inter-Visit Period				0.071	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.110	-0.147	-0.165		
[95% CI]	[-0.151, -0.069]	[-0.185, -0.108]	[-0.225, -0.106]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.037 [-0.020, 0.093] 0.206
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.055 [-0.017, 0.128] 0.134
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.090, 0.052] 0.603

Produced: 17 December 2020 Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.190	-0.207	-0.198		
[95% CI]	[-0.238, -0.142]	[-0.251, -0.162]	[-0.267, -0.129]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.017 [-0.049, 0.082] 0.620
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.076, 0.091] 0.860
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.073, 0.091] 0.829
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.212	-0.238	-0.217		
[95% CI]	[-0.264, -0.159]	[-0.287, -0.189]	[-0.292, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.026 [-0.046, 0.098] 0.475
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.087, 0.097] 0.913
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.021 [-0.069, 0.111] 0.647

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.249	-0.227	-0.239		
[95% CI]	[-0.307, -0.191]	[-0.281, -0.173]	[-0.322, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.022 [-0.101, 0.058] 0.592
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.112, 0.092] 0.846
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.111, 0.088] 0.818
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.259	-0.223	-0.199		
[95% CI]	[-0.322, -0.196]	[-0.282, -0.164]	[-0.289, -0.108]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.122, 0.050] 0.414
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.060 [-0.170, 0.051] 0.287
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.084, 0.132] 0.664

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.189	-0.214	-0.203		
[95% CI]	[-0.236, -0.143]	[-0.257, -0.171]	[-0.269, -0.137]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.025 [-0.038, 0.088] 0.440
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.067, 0.094] 0.741
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.068, 0.090] 0.781
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.221	-0.220	-0.212		
[95% CI]	[-0.271, -0.171]	[-0.266, -0.173]	[-0.284, -0.140]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.070, 0.067] 0.961
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.097, 0.078] 0.828
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.078, 0.094] 0.855

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.898	
Inter-Visit Period				0.105	
Treatment*Inter-Visit Period				0.106	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.067	-0.085	-0.129		
[95% CI]	[-0.109, -0.024]	[-0.125, -0.045]	[-0.190, -0.068]		
p-value	0.002**	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.018 [-0.040, 0.076] 0.543
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.062 [-0.012, 0.137] 0.099
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-0.117, 0.028] 0.231

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.137	-0.122	-0.152		
[95% CI]	[-0.184, -0.090]	[-0.166, -0.078]	[-0.219, -0.084]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.079, 0.049] 0.641
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.067, 0.097] 0.725
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.110, 0.050] 0.465
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.163	-0.151	-0.155		
[95% CI]	[-0.216, -0.109]	[-0.201, -0.101]	[-0.232, -0.078]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.085, 0.062] 0.758
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.101, 0.086] 0.878
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.096, 0.088] 0.929

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.189	-0.162	-0.151		
[95% CI]	[-0.246, -0.132]	[-0.215, -0.108]	[-0.233, -0.069]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.105, 0.051] 0.498
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.038 [-0.138, 0.062] 0.456
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.087, 0.109] 0.826
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.200	-0.161	-0.111		
[95% CI]	[-0.261, -0.138]	[-0.219, -0.103]	[-0.200, -0.022]		
p-value	<0.001***	<0.001***	0.015*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.124, 0.046] 0.371
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.089 [-0.197, 0.020] 0.110
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.050 [-0.057, 0.156] 0.358

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.140	-0.132	-0.150		
[95% CI]	[-0.187, -0.093]	[-0.175, -0.088]	[-0.217, -0.083]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.072, 0.056] 0.803
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.071, 0.092] 0.807
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.098, 0.062] 0.653
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.167	-0.147	-0.141		
[95% CI]	[-0.217, -0.116]	[-0.194, -0.099]	[-0.214, -0.069]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.089, 0.049] 0.565
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.114, 0.063] 0.570
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.081, 0.092] 0.904

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.483	
Inter-Visit Period				0.023*	
Treatment*Inter-Visit Period				0.325	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.100	-0.114	-0.170		
[95% CI]	[-0.142, -0.058]	[-0.153, -0.076]	[-0.229, -0.110]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.043, 0.071] 0.623
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.069 [-0.003, 0.142] 0.062
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.055 [-0.127, 0.016] 0.129

Produced: 17 December 2020 Page 17 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.172	-0.154	-0.215		
[95% CI]	[-0.221, -0.122]	[-0.200, -0.107]	[-0.286, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.086, 0.051] 0.611
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.043 [-0.044, 0.130] 0.330
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.146, 0.025] 0.162
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.215	-0.175	-0.225		
[95% CI]	[-0.270, -0.159]	[-0.227, -0.123]	[-0.305, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.116, 0.036] 0.305
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.087, 0.108] 0.831
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.050 [-0.146, 0.045] 0.300

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.239	-0.180	-0.212		
[95% CI]	[-0.300, -0.178]	[-0.237, -0.124]	[-0.299, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.142, 0.024] 0.166
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.027 [-0.134, 0.079] 0.616
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.136, 0.073] 0.553
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.252	-0.178	-0.190		
[95% CI]	[-0.317, -0.186]	[-0.240, -0.117]	[-0.284, -0.096]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.163, 0.016] 0.108
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.061 [-0.176, 0.053] 0.292
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.124, 0.100] 0.835

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.184	-0.159	-0.214		
[95% CI]	[-0.233, -0.135]	[-0.205, -0.114]	[-0.284, -0.144]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.091, 0.042] 0.468
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.030 [-0.056, 0.115] 0.494
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.138, 0.029] 0.202
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.214	-0.169	-0.208		
[95% CI]	[-0.267, -0.161]	[-0.219, -0.120]	[-0.284, -0.131]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.118, 0.028] 0.224
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.100, 0.086] 0.888
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.130, 0.053] 0.408

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.208	
Inter-Visit Period				0.235	
Treatment*Inter-Visit Period				0.316	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.135	-0.104	-0.142		
[95% CI]	[-0.179, -0.092]	[-0.145, -0.064]	[-0.205, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.090, 0.029] 0.310
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.069, 0.083] 0.855
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.112, 0.037] 0.318

Produced: 17 December 2020 Page 21 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.212	-0.152	-0.213		
[95% CI]	[-0.261, -0.163]	[-0.198, -0.106]	[-0.284, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.127, 0.007] 0.079
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.084, 0.087] 0.973
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.145, 0.022] 0.150
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.234	-0.194	-0.256		
[95% CI]	[-0.289, -0.180]	[-0.245, -0.143]	[-0.334, -0.178]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.115, 0.034] 0.291
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.073, 0.117] 0.653
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.062 [-0.155, 0.031] 0.193

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.274	-0.209	-0.254		
[95% CI]	[-0.333, -0.215]	[-0.265, -0.154]	[-0.339, -0.169]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.065 [-0.146, 0.016] 0.118
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.020 [-0.123, 0.084] 0.712
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.045 [-0.147, 0.057] 0.385
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.280	-0.194	-0.221		
[95% CI]	[-0.344, -0.217]	[-0.254, -0.135]	[-0.312, -0.129]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.173, 0.001] 0.053
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.060 [-0.171, 0.052] 0.295
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.136, 0.083] 0.635

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.212	-0.167	-0.225		
[95% CI]	[-0.260, -0.165]	[-0.212, -0.123]	[-0.294, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.110, 0.020] 0.177
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.070, 0.097] 0.754
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.058 [-0.140, 0.024] 0.163
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.244	-0.185	-0.232		
[95% CI]	[-0.296, -0.193]	[-0.233, -0.137]	[-0.306, -0.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.130, 0.011] 0.096
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-0.102, 0.078] 0.787
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.135, 0.041] 0.292

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	359	325	184		
Effect					
Treatment				0.801	
Inter-Visit Period				0.106	
Treatment*Inter-Visit Period				0.948	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.131	-0.120	-0.130		
[95% CI]	[-0.159, -0.104]	[-0.149, -0.091]	[-0.169, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.051, 0.029] 0.578
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.048, 0.046] 0.971
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.058, 0.038] 0.670

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.175	-0.167	-0.181		
[95% CI]	[-0.209, -0.140]	[-0.203, -0.131]	[-0.229, -0.133]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.057, 0.042] 0.769
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.053, 0.065] 0.837
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.074, 0.047] 0.656
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.211	-0.194	-0.224		
[95% CI]	[-0.250, -0.173]	[-0.234, -0.153]	[-0.278, -0.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.073, 0.038] 0.528
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.053, 0.079] 0.703
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.097, 0.036] 0.370

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.219	-0.212	-0.237		
[95% CI]	[-0.260, -0.177]	[-0.255, -0.168]	[-0.296, -0.179]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.067, 0.053] 0.813
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.053, 0.090] 0.611
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.098, 0.047] 0.487
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.223	-0.212	-0.229		
[95% CI]	[-0.265, -0.181]	[-0.257, -0.168]	[-0.288, -0.170]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.072, 0.051] 0.734
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.067, 0.079] 0.875
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.090, 0.058] 0.663

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.188	-0.174	-0.196		
[95% CI]	[-0.221, -0.154]	[-0.209, -0.139]	[-0.243, -0.149]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.062, 0.035] 0.583
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.049, 0.066] 0.769
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.081, 0.037] 0.457
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.204	-0.193	-0.215		
[95% CI]	[-0.241, -0.168]	[-0.231, -0.155]	[-0.266, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.064, 0.041] 0.676
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.052, 0.073] 0.738
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.085, 0.042] 0.500

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	359	325	184		
Effect					
Treatment				0.931	
Inter-Visit Period				0.040*	
Treatment*Inter-Visit Period				0.750	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.142	-0.142	-0.126		
[95% CI]	[-0.174, -0.110]	[-0.175, -0.108]	[-0.171, -0.082]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.047, 0.046] 0.989
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.071, 0.039] 0.570
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.016 [-0.040, 0.071] 0.584

Produced: 17 December 2020 Page 29 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.197	-0.199	-0.192		
[95% CI]	[-0.237, -0.158]	[-0.240, -0.157]	[-0.248, -0.137]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.056, 0.059] 0.953
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.073, 0.063] 0.884
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.007 [-0.062, 0.076] 0.847
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.252	-0.237	-0.251		
[95% CI]	[-0.294, -0.209]	[-0.282, -0.192]	[-0.311, -0.191]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.077, 0.048] 0.649
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.074, 0.073] 0.987
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.089, 0.061] 0.719

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.259	-0.252	-0.261		
[95% CI]	[-0.305, -0.213]	[-0.300, -0.204]	[-0.325, -0.197]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.074, 0.059] 0.827
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.077, 0.081] 0.964
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.090, 0.071] 0.822
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.267	-0.246	-0.233		
[95% CI]	[-0.314, -0.220]	[-0.295, -0.197]	[-0.299, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.089, 0.047] 0.545
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.034 [-0.115, 0.047] 0.408
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.013 [-0.069, 0.095] 0.754

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.218	-0.211	-0.214		
[95% CI]	[-0.255, -0.180]	[-0.250, -0.171]	[-0.266, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.062, 0.047] 0.793
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.069, 0.060] 0.895
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.069, 0.063] 0.930
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.240	-0.230	-0.231		
[95% CI]	[-0.280, -0.200]	[-0.272, -0.188]	[-0.287, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.068, 0.047] 0.723
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.078, 0.059] 0.785
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.071, 0.069] 0.979

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	359	325	184		
Effect					
Treatment				0.489	
Inter-Visit Period				0.216	
Treatment*Inter-Visit Period				0.952	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.150	-0.129	-0.164		
[95% CI]	[-0.181, -0.119]	[-0.162, -0.096]	[-0.207, -0.120]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.066, 0.024] 0.361
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.040, 0.067] 0.618
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.089, 0.020] 0.212

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.190	-0.186	-0.220		
[95% CI]	[-0.228, -0.152]	[-0.226, -0.145]	[-0.274, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.060, 0.051] 0.882
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.030 [-0.036, 0.097] 0.366
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.102, 0.033] 0.312
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.220	-0.209	-0.253		
[95% CI]	[-0.263, -0.178]	[-0.253, -0.165]	[-0.312, -0.193]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.073, 0.050] 0.711
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.032 [-0.041, 0.105] 0.387
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-0.117, 0.030] 0.247

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.223	-0.227	-0.267		
[95% CI]	[-0.269, -0.178]	[-0.274, -0.179]	[-0.330, -0.203]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.062, 0.069] 0.917
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.044 [-0.035, 0.122] 0.275
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.120, 0.040] 0.324
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.227	-0.227	-0.266		
[95% CI]	[-0.273, -0.181]	[-0.276, -0.179]	[-0.330, -0.201]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.000 [-0.066, 0.067] 0.998
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.039 [-0.041, 0.118] 0.340
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.119, 0.042] 0.349

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.200	-0.189	-0.229		
[95% CI]	[-0.237, -0.163]	[-0.228, -0.151]	[-0.281, -0.177]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.064, 0.043] 0.694
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.029 [-0.035, 0.092] 0.376
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.104, 0.025] 0.232
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.213	-0.208	-0.248		
[95% CI]	[-0.252, -0.173]	[-0.250, -0.167]	[-0.303, -0.192]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.062, 0.053] 0.880
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.033, 0.103] 0.315
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.109, 0.030] 0.267

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	359	325	184		
Effect					
Treatment				0.875	
Inter-Visit Period				0.068	
Treatment*Inter-Visit Period				0.929	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.100	-0.096	-0.107		
[95% CI]	[-0.131, -0.069]	[-0.129, -0.064]	[-0.151, -0.064]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.048, 0.042] 0.883
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.046, 0.061] 0.776
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.065, 0.043] 0.688

Produced: 17 December 2020 Page 37 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.134	-0.122	-0.142		
[95% CI]	[-0.172, -0.096]	[-0.162, -0.082]	[-0.196, -0.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.068, 0.042] 0.653
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.057, 0.074] 0.807
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.087, 0.046] 0.540
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.162	-0.151	-0.175		
[95% CI]	[-0.203, -0.120]	[-0.195, -0.107]	[-0.234, -0.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.071, 0.050] 0.736
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.058, 0.086] 0.708
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.097, 0.049] 0.517

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.161	-0.170	-0.189		
[95% CI]	[-0.207, -0.115]	[-0.218, -0.122]	[-0.253, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.058, 0.075] 0.797
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.052, 0.107] 0.497
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.099, 0.062] 0.649
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.163	-0.172	-0.179		
[95% CI]	[-0.210, -0.117]	[-0.221, -0.123]	[-0.244, -0.113]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.059, 0.076] 0.799
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.065, 0.095] 0.711
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.088, 0.075] 0.878

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.144	-0.134	-0.155		
[95% CI]	[-0.180, -0.107]	[-0.172, -0.095]	[-0.206, -0.103]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.063, 0.043] 0.713
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.052, 0.074] 0.731
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.086, 0.043] 0.521
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.153	-0.152	-0.169		
[95% CI]	[-0.193, -0.113]	[-0.194, -0.110]	[-0.225, -0.113]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.059, 0.057] 0.983
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.052, 0.085] 0.639
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.087, 0.053] 0.632

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	359	325	184		
Effect					
Treatment				0.589	
Inter-Visit Period				0.004**	
Treatment*Inter-Visit Period				0.870	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.132	-0.113	-0.124		
[95% CI]	[-0.164, -0.101]	[-0.146, -0.079]	[-0.168, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.066, 0.026] 0.399
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.063, 0.046] 0.767
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.067, 0.044] 0.683

Produced: 17 December 2020 Page 41 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates
 [2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.177	-0.162	-0.168		
[95% CI]	[-0.216, -0.138]	[-0.203, -0.122]	[-0.222, -0.113]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.071, 0.042] 0.617
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.076, 0.058] 0.786
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.073, 0.063] 0.883
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.213	-0.178	-0.217		
[95% CI]	[-0.256, -0.169]	[-0.223, -0.132]	[-0.278, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.098, 0.028] 0.274
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.070, 0.079] 0.903
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.115, 0.036] 0.305

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.233	-0.199	-0.234		
[95% CI]	[-0.279, -0.186]	[-0.248, -0.150]	[-0.299, -0.169]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.101, 0.034] 0.326
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.079, 0.081] 0.978
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.116, 0.047] 0.401
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.236	-0.204	-0.238		
[95% CI]	[-0.284, -0.189]	[-0.254, -0.155]	[-0.305, -0.172]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.100, 0.037] 0.368
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.079, 0.084] 0.954
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.034 [-0.117, 0.049] 0.423

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.189	-0.163	-0.188		
[95% CI]	[-0.227, -0.151]	[-0.203, -0.123]	[-0.241, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.081, 0.029] 0.348
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.067, 0.064] 0.961
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.091, 0.042] 0.466
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.212	-0.182	-0.212		
[95% CI]	[-0.252, -0.171]	[-0.225, -0.140]	[-0.269, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.030 [-0.088, 0.029] 0.325
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.070, 0.070] 0.999
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.101, 0.041] 0.414

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	359	324	184		
Effect					
Treatment				0.981	
Inter-Visit Period				0.027*	
Treatment*Inter-Visit Period				0.938	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.140	-0.123	-0.131		
[95% CI]	[-0.173, -0.107]	[-0.158, -0.089]	[-0.177, -0.085]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.065, 0.031] 0.488
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.066, 0.047] 0.742
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.065, 0.050] 0.800

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.200	-0.191	-0.188		
[95% CI]	[-0.241, -0.159]	[-0.234, -0.148]	[-0.245, -0.130]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.069, 0.050] 0.757
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.013 [-0.083, 0.058] 0.721
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.068, 0.075] 0.925
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.236	-0.225	-0.227		
[95% CI]	[-0.280, -0.192]	[-0.271, -0.178]	[-0.289, -0.165]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.075, 0.053] 0.728
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.085, 0.067] 0.808
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.079, 0.075] 0.961

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.236	-0.246	-0.240		
[95% CI]	[-0.283, -0.188]	[-0.297, -0.196]	[-0.307, -0.174]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.058, 0.080] 0.759
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.077, 0.087] 0.908
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.006 [-0.078, 0.090] 0.888
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.242	-0.244	-0.244		
[95% CI]	[-0.290, -0.194]	[-0.295, -0.194]	[-0.311, -0.176]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.068, 0.071] 0.962
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.081, 0.084] 0.973
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.000 [-0.084, 0.084] 0.995

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12b Statistical Analysis of Average Daily Asthma Symptoms score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.210	-0.199	-0.200		
[95% CI]	[-0.250, -0.171]	[-0.240, -0.157]	[-0.255, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.069, 0.046] 0.690
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.078, 0.057] 0.761
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.070, 0.068] 0.974
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.225	-0.222	-0.221		
[95% CI]	[-0.266, -0.183]	[-0.266, -0.178]	[-0.279, -0.163]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.063, 0.058] 0.936
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.075, 0.068] 0.921
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.072, 0.074] 0.976

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: < 25					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.485	
Inter-Visit Period				0.263	
Treatment*Inter-Visit Period				0.773	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.119	-0.110	-0.119		
[95% CI]	[-0.164, -0.074]	[-0.153, -0.066]	[-0.184, -0.055]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.072, 0.053] 0.762
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.079, 0.079] 1.000
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.087, 0.068] 0.807

Produced: 17 December 2020 Page 1 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.177	-0.141	-0.167		
[95% CI]	[-0.228, -0.125]	[-0.191, -0.092]	[-0.240, -0.093]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.107, 0.036] 0.326
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.100, 0.080] 0.824
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.114, 0.063] 0.572
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.200	-0.164	-0.224		
[95% CI]	[-0.258, -0.142]	[-0.220, -0.108]	[-0.307, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.117, 0.044] 0.377
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.078, 0.125] 0.645
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.060 [-0.160, 0.040] 0.239

Produced: 17 December 2020

Page 2 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.224	-0.177	-0.236		
[95% CI]	[-0.287, -0.161]	[-0.237, -0.117]	[-0.326, -0.147]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.134, 0.039] 0.283
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.097, 0.122] 0.827
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.060 [-0.168, 0.048] 0.278
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.237	-0.177	-0.238		
[95% CI]	[-0.303, -0.171]	[-0.240, -0.114]	[-0.333, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.151, 0.032] 0.200
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.114, 0.117] 0.981
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.175, 0.053] 0.293

Produced: 17 December 2020

Page 3 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.181	-0.149	-0.190		
[95% CI]	[-0.232, -0.130]	[-0.197, -0.100]	[-0.263, -0.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.103, 0.039] 0.374
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.079, 0.099] 0.831
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.042 [-0.129, 0.046] 0.352
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.205	-0.163	-0.214		
[95% CI]	[-0.260, -0.150]	[-0.216, -0.110]	[-0.293, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.119, 0.034] 0.274
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.088, 0.105] 0.863
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.051 [-0.146, 0.044] 0.292

Produced: 17 December 2020

Page 4 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.703	
Inter-Visit Period				0.077	
Treatment*Inter-Visit Period				0.622	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.135	-0.135	-0.145		
[95% CI]	[-0.186, -0.084]	[-0.184, -0.087]	[-0.218, -0.073]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.070, 0.071] 0.988
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.078, 0.099] 0.818
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.097, 0.078] 0.825

Produced: 17 December 2020 Page 5 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.186	-0.173	-0.181		
[95% CI]	[-0.246, -0.126]	[-0.230, -0.115]	[-0.267, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.097, 0.070] 0.751
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.110, 0.100] 0.928
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.112, 0.095] 0.871
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.220	-0.195	-0.239		
[95% CI]	[-0.286, -0.154]	[-0.258, -0.131]	[-0.334, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.117, 0.066] 0.582
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.096, 0.134] 0.742
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.045 [-0.158, 0.068] 0.437

Produced: 17 December 2020

Page 6 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.257	-0.219	-0.258		
[95% CI]	[-0.327, -0.188]	[-0.285, -0.153]	[-0.358, -0.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.134, 0.058] 0.435
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.121, 0.122] 0.992
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.159, 0.081] 0.524
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.288	-0.207	-0.246		
[95% CI]	[-0.362, -0.215]	[-0.277, -0.137]	[-0.352, -0.140]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.081 [-0.182, 0.021] 0.118
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.042 [-0.171, 0.086] 0.518
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.165, 0.088] 0.551

Produced: 17 December 2020

Page 7 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.197	-0.179	-0.207		
[95% CI]	[-0.254, -0.139]	[-0.234, -0.124]	[-0.289, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.097, 0.062] 0.660
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.090, 0.111] 0.837
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.127, 0.071] 0.574
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.234	-0.196	-0.230		
[95% CI]	[-0.295, -0.173]	[-0.254, -0.138]	[-0.317, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.122, 0.046] 0.376
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.110, 0.102] 0.936
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.034 [-0.138, 0.071] 0.529

Produced: 17 December 2020

Page 8 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.656	
Inter-Visit Period				0.529	
Treatment*Inter-Visit Period				0.707	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.132	-0.130	-0.152		
[95% CI]	[-0.184, -0.080]	[-0.181, -0.080]	[-0.227, -0.077]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.074, 0.071] 0.970
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.071, 0.112] 0.666
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.112, 0.069] 0.641

Produced: 17 December 2020 Page 9 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.173	-0.172	-0.196		
[95% CI]	[-0.234, -0.113]	[-0.230, -0.115]	[-0.282, -0.110]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.084, 0.082] 0.984
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.082, 0.128] 0.671
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.127, 0.080] 0.655
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.186	-0.194	-0.248		
[95% CI]	[-0.252, -0.121]	[-0.257, -0.132]	[-0.341, -0.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.083, 0.099] 0.860
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.061 [-0.053, 0.176] 0.292
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.053 [-0.166, 0.060] 0.354

Produced: 17 December 2020 Page 10 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.217	-0.196	-0.262		
[95% CI]	[-0.287, -0.147]	[-0.263, -0.130]	[-0.361, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.117, 0.076] 0.672
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.044 [-0.078, 0.166] 0.475
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.065 [-0.185, 0.055] 0.287
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.237	-0.190	-0.258		
[95% CI]	[-0.310, -0.164]	[-0.260, -0.121]	[-0.363, -0.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.147, 0.054] 0.361
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.106, 0.149] 0.742
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.068 [-0.193, 0.057] 0.287

Produced: 17 December 2020 Page 11 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.174	-0.178	-0.217		
[95% CI]	[-0.232, -0.116]	[-0.233, -0.122]	[-0.300, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.076, 0.084] 0.924
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.043 [-0.058, 0.144] 0.402
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.139, 0.060] 0.440
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.200	-0.186	-0.239		
[95% CI]	[-0.262, -0.139]	[-0.245, -0.127]	[-0.327, -0.150]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.100, 0.071] 0.739
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [-0.069, 0.146] 0.483
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.053 [-0.159, 0.053] 0.327

Produced: 17 December 2020 Page 12 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.438	
Inter-Visit Period				0.459	
Treatment*Inter-Visit Period				0.846	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.093	-0.072	-0.066		
[95% CI]	[-0.145, -0.041]	[-0.122, -0.023]	[-0.140, 0.008]		
p-value	<0.001***	0.004**	0.081		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.092, 0.051] 0.572
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.027 [-0.117, 0.063] 0.558
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.006 [-0.083, 0.096] 0.888

Produced: 17 December 2020 Page 13 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.161	-0.094	-0.113		
[95% CI]	[-0.221, -0.101]	[-0.151, -0.037]	[-0.199, -0.027]		
p-value	<0.001***	0.001**	0.010**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.067 [-0.150, 0.015] 0.110
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.048 [-0.153, 0.056] 0.363
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.122, 0.084] 0.717
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.184	-0.122	-0.162		
[95% CI]	[-0.249, -0.119]	[-0.184, -0.060]	[-0.255, -0.070]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.062 [-0.152, 0.028] 0.174
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.135, 0.092] 0.711
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.041 [-0.152, 0.071] 0.471

Produced: 17 December 2020 Page 14 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.193	-0.134	-0.180		
[95% CI]	[-0.263, -0.123]	[-0.201, -0.067]	[-0.280, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.156, 0.038] 0.231
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.013 [-0.136, 0.109] 0.831
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.046 [-0.167, 0.075] 0.456
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.200	-0.147	-0.184		
[95% CI]	[-0.273, -0.127]	[-0.217, -0.078]	[-0.289, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.053 [-0.154, 0.047] 0.300
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.143, 0.112] 0.807
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.037 [-0.163, 0.088] 0.560

Produced: 17 December 2020 Page 15 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.163	-0.105	-0.132		
[95% CI]	[-0.221, -0.105]	[-0.161, -0.050]	[-0.215, -0.050]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.138, 0.023] 0.159
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.031 [-0.132, 0.070] 0.552
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.127, 0.073] 0.596
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.180	-0.123	-0.157		
[95% CI]	[-0.242, -0.118]	[-0.182, -0.064]	[-0.246, -0.069]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.143, 0.029] 0.192
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.131, 0.086] 0.682
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.034 [-0.141, 0.072] 0.526

Produced: 17 December 2020 Page 16 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.240	
Inter-Visit Period				0.106	
Treatment*Inter-Visit Period				0.457	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.115	-0.101	-0.115		
[95% CI]	[-0.166, -0.064]	[-0.149, -0.052]	[-0.188, -0.042]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.085, 0.056] 0.685
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.089, 0.089] 0.997
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.102, 0.073] 0.748

Produced: 17 December 2020 Page 17 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.185	-0.126	-0.177		
[95% CI]	[-0.243, -0.127]	[-0.182, -0.071]	[-0.260, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.139, 0.021] 0.149
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.109, 0.093] 0.881
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.051 [-0.151, 0.048] 0.312
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.212	-0.146	-0.248		
[95% CI]	[-0.277, -0.147]	[-0.208, -0.084]	[-0.340, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.066 [-0.156, 0.024] 0.147
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.078, 0.149] 0.541
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.102 [-0.213, 0.010] 0.074

Produced: 17 December 2020 Page 18 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.233	-0.158	-0.248		
[95% CI]	[-0.305, -0.161]	[-0.226, -0.089]	[-0.351, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.075 [-0.175, 0.024] 0.137
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.110, 0.141] 0.812
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.090 [-0.214, 0.033] 0.151
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.227	-0.163	-0.268		
[95% CI]	[-0.302, -0.153]	[-0.235, -0.092]	[-0.376, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.064 [-0.168, 0.039] 0.224
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.041 [-0.090, 0.172] 0.541
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.105 [-0.234, 0.024] 0.111

Produced: 17 December 2020 Page 19 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.189	-0.133	-0.206		
[95% CI]	[-0.246, -0.132]	[-0.187, -0.079]	[-0.287, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.056 [-0.135, 0.022] 0.161
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.083, 0.116] 0.742
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.073 [-0.171, 0.025] 0.144
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.210	-0.147	-0.231		
[95% CI]	[-0.272, -0.147]	[-0.206, -0.087]	[-0.320, -0.142]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.063 [-0.149, 0.023] 0.150
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.087, 0.130] 0.693
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.085 [-0.192, 0.022] 0.120

Produced: 17 December 2020 Page 20 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.324	
Inter-Visit Period				0.051	
Treatment*Inter-Visit Period				0.976	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.134	-0.096	-0.128		
[95% CI]	[-0.187, -0.081]	[-0.147, -0.045]	[-0.204, -0.052]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.112, 0.035] 0.308
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.099, 0.087] 0.899
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.124, 0.060] 0.489

Produced: 17 December 2020 Page 21 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.187	-0.125	-0.183		
[95% CI]	[-0.249, -0.126]	[-0.184, -0.066]	[-0.271, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.062 [-0.148, 0.023] 0.151
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.112, 0.103] 0.935
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.058 [-0.164, 0.048] 0.284
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.213	-0.155	-0.231		
[95% CI]	[-0.280, -0.146]	[-0.219, -0.091]	[-0.327, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.152, 0.034] 0.214
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.099, 0.135] 0.767
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.076 [-0.192, 0.039] 0.193

Produced: 17 December 2020 Page 22 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.229	-0.171	-0.231		
[95% CI]	[-0.301, -0.157]	[-0.240, -0.102]	[-0.334, -0.128]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.058 [-0.158, 0.041] 0.251
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.124, 0.128] 0.976
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.060 [-0.184, 0.064] 0.341
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.236	-0.177	-0.249		
[95% CI]	[-0.311, -0.161]	[-0.249, -0.105]	[-0.358, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.163, 0.045] 0.265
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.118, 0.146] 0.840
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.073 [-0.203, 0.057] 0.273

Produced: 17 December 2020 Page 23 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.193	-0.136	-0.200		
[95% CI]	[-0.252, -0.134]	[-0.193, -0.080]	[-0.285, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.139, 0.025] 0.175
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.096, 0.111] 0.891
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.166, 0.038] 0.219
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.213	-0.155	-0.220		
[95% CI]	[-0.276, -0.149]	[-0.215, -0.095]	[-0.310, -0.129]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.058 [-0.145, 0.030] 0.196
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.103, 0.118] 0.897
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.065 [-0.174, 0.044] 0.242

Produced: 17 December 2020 Page 24 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: [25-30)					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.978	
Inter-Visit Period				0.082	
Treatment*Inter-Visit Period				0.157	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.141	-0.142	-0.180		
[95% CI]	[-0.177, -0.105]	[-0.180, -0.105]	[-0.231, -0.130]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.051, 0.053] 0.970
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.039 [-0.023, 0.102] 0.214
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.101, 0.025] 0.232

Produced: 17 December 2020 Page 25 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.200	-0.202	-0.223		
[95% CI]	[-0.245, -0.155]	[-0.249, -0.156]	[-0.286, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.062, 0.067] 0.934
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.055, 0.100] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.099, 0.058] 0.613
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.245	-0.243	-0.246		
[95% CI]	[-0.294, -0.196]	[-0.294, -0.192]	[-0.315, -0.177]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.073, 0.069] 0.955
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.084, 0.086] 0.989
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.089, 0.083] 0.952

Produced: 17 December 2020 Page 26 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.266	-0.265	-0.236		
[95% CI]	[-0.318, -0.213]	[-0.320, -0.210]	[-0.311, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.077, 0.076] 0.987
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.029 [-0.121, 0.062] 0.530
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.029 [-0.064, 0.121] 0.545
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.291	-0.278	-0.217		
[95% CI]	[-0.345, -0.236]	[-0.335, -0.221]	[-0.294, -0.139]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.091, 0.066] 0.758
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.074 [-0.169, 0.020] 0.124
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.062 [-0.034, 0.158] 0.207

Produced: 17 December 2020 Page 27 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.215	-0.215	-0.229		
[95% CI]	[-0.259, -0.172]	[-0.260, -0.170]	[-0.290, -0.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.063, 0.063] 0.998
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.062, 0.088] 0.725
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.089, 0.062] 0.727
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.246	-0.243	-0.228		
[95% CI]	[-0.293, -0.199]	[-0.292, -0.195]	[-0.294, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.070, 0.064] 0.929
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.099, 0.062] 0.657
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.066, 0.097] 0.715

Produced: 17 December 2020 Page 28 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.682	
Inter-Visit Period				0.138	
Treatment*Inter-Visit Period				0.588	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.152	-0.150	-0.146		
[95% CI]	[-0.194, -0.110]	[-0.194, -0.107]	[-0.205, -0.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.062, 0.059] 0.963
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.078, 0.067] 0.878
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.069, 0.077] 0.911

Produced: 17 December 2020 Page 29 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.227	-0.224	-0.216		
[95% CI]	[-0.279, -0.175]	[-0.278, -0.170]	[-0.289, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.079, 0.071] 0.922
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-0.102, 0.078] 0.800
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.083, 0.099] 0.865
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.279	-0.271	-0.258		
[95% CI]	[-0.334, -0.224]	[-0.328, -0.213]	[-0.336, -0.180]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.088, 0.071] 0.836
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.117, 0.075] 0.667
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.013 [-0.084, 0.109] 0.800

Produced: 17 December 2020 Page 30 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.289	-0.287	-0.242		
[95% CI]	[-0.347, -0.230]	[-0.348, -0.227]	[-0.324, -0.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.085, 0.083] 0.979
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.047 [-0.148, 0.054] 0.361
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.046 [-0.057, 0.148] 0.380
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.317	-0.298	-0.224		
[95% CI]	[-0.376, -0.257]	[-0.360, -0.236]	[-0.308, -0.139]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.105, 0.067] 0.669
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.093 [-0.197, 0.011] 0.078
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.074 [-0.031, 0.179] 0.165

Produced: 17 December 2020 Page 31 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.244	-0.238	-0.228		
[95% CI]	[-0.292, -0.195]	[-0.288, -0.187]	[-0.296, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.006 [-0.076, 0.064] 0.868
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.099, 0.068] 0.712
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.010 [-0.075, 0.094] 0.820
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.273	-0.265	-0.231		
[95% CI]	[-0.323, -0.222]	[-0.318, -0.212]	[-0.302, -0.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.081, 0.066] 0.838
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.042 [-0.130, 0.046] 0.347
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.034 [-0.054, 0.123] 0.447

Produced: 17 December 2020 Page 32 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.804	
Inter-Visit Period				0.482	
Treatment*Inter-Visit Period				0.390	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.158	-0.155	-0.219		
[95% CI]	[-0.199, -0.117]	[-0.198, -0.113]	[-0.276, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.062, 0.056] 0.922
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.061 [-0.010, 0.131] 0.092
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.135, 0.008] 0.081

Produced: 17 December 2020 Page 33 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.218	-0.216	-0.272		
[95% CI]	[-0.267, -0.169]	[-0.267, -0.165]	[-0.341, -0.203]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.073, 0.068] 0.946
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.054 [-0.031, 0.138] 0.215
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.142, 0.030] 0.200
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.255	-0.262	-0.281		
[95% CI]	[-0.309, -0.202]	[-0.318, -0.206]	[-0.357, -0.206]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.071, 0.084] 0.872
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.026 [-0.067, 0.119] 0.584
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.114, 0.075] 0.684

Produced: 17 December 2020 Page 34 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.271	-0.277	-0.288		
[95% CI]	[-0.330, -0.213]	[-0.338, -0.217]	[-0.370, -0.205]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.078, 0.090] 0.889
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.085, 0.117] 0.750
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.113, 0.092] 0.842
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.296	-0.290	-0.266		
[95% CI]	[-0.355, -0.237]	[-0.352, -0.229]	[-0.349, -0.182]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.091, 0.080] 0.900
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.030 [-0.133, 0.072] 0.562
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.080, 0.129] 0.641

Produced: 17 December 2020 Page 35 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.229	-0.231	-0.269		
[95% CI]	[-0.276, -0.182]	[-0.280, -0.182]	[-0.335, -0.202]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.066, 0.070] 0.949
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.040 [-0.042, 0.121] 0.339
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.120, 0.045] 0.373
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.256	-0.257	-0.273		
[95% CI]	[-0.307, -0.205]	[-0.310, -0.205]	[-0.345, -0.202]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.072, 0.075] 0.969
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.070, 0.105] 0.698
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.105, 0.073] 0.726

Produced: 17 December 2020 Page 36 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.819	
Inter-Visit Period				0.355	
Treatment*Inter-Visit Period				0.065	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.101	-0.121	-0.161		
[95% CI]	[-0.143, -0.060]	[-0.164, -0.078]	[-0.218, -0.103]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.020 [-0.040, 0.079] 0.513
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.059 [-0.012, 0.130] 0.101
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.111, 0.032] 0.280

Produced: 17 December 2020 Page 37 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.146	-0.164	-0.183		
[95% CI]	[-0.195, -0.097]	[-0.215, -0.114]	[-0.252, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.018 [-0.052, 0.088] 0.611
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.037 [-0.047, 0.121] 0.384
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.104, 0.066] 0.659
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.188	-0.202	-0.178		
[95% CI]	[-0.242, -0.133]	[-0.258, -0.146]	[-0.255, -0.102]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.064, 0.093] 0.722
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.103, 0.084] 0.845
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.071, 0.119] 0.626

Produced: 17 December 2020 Page 38 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.208	-0.230	-0.171		
[95% CI]	[-0.266, -0.149]	[-0.291, -0.169]	[-0.253, -0.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.022 [-0.062, 0.106] 0.606
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.037 [-0.138, 0.064] 0.474
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.059 [-0.043, 0.161] 0.258
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.233	-0.245	-0.150		
[95% CI]	[-0.293, -0.172]	[-0.308, -0.182]	[-0.235, -0.064]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.074, 0.099] 0.778
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.083 [-0.187, 0.021] 0.118
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.096 [-0.010, 0.201] 0.076

Produced: 17 December 2020 Page 39 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.162	-0.178	-0.177		
[95% CI]	[-0.209, -0.114]	[-0.227, -0.129]	[-0.244, -0.110]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.016 [-0.052, 0.085] 0.641
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.066, 0.098] 0.709
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.082, 0.084] 0.986
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.190	-0.207	-0.169		
[95% CI]	[-0.242, -0.139]	[-0.261, -0.154]	[-0.241, -0.097]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.017 [-0.057, 0.091] 0.652
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.110, 0.067] 0.636
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.038 [-0.051, 0.128] 0.401

Produced: 17 December 2020 Page 40 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.839	
Inter-Visit Period				0.002**	
Treatment*Inter-Visit Period				0.067	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.153	-0.141	-0.195		
[95% CI]	[-0.194, -0.112]	[-0.183, -0.098]	[-0.252, -0.137]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.071, 0.047] 0.692
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.042 [-0.029, 0.112] 0.244
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.125, 0.018] 0.139

Produced: 17 December 2020 Page 41 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.207	-0.205	-0.217		
[95% CI]	[-0.259, -0.154]	[-0.260, -0.151]	[-0.291, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.077, 0.074] 0.971
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.081, 0.101] 0.828
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.103, 0.080] 0.806
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.259	-0.239	-0.262		
[95% CI]	[-0.316, -0.202]	[-0.298, -0.180]	[-0.342, -0.182]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.102, 0.062] 0.631
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.096, 0.100] 0.964
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.122, 0.077] 0.660

Produced: 17 December 2020 Page 42 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.296	-0.267	-0.241		
[95% CI]	[-0.357, -0.235]	[-0.331, -0.204]	[-0.327, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.117, 0.059] 0.516
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.055 [-0.161, 0.050] 0.304
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.026 [-0.081, 0.133] 0.631
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.318	-0.281	-0.224		
[95% CI]	[-0.381, -0.255]	[-0.346, -0.215]	[-0.314, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.128, 0.054] 0.419
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.094 [-0.203, 0.015] 0.092
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.056 [-0.054, 0.167] 0.317

Produced: 17 December 2020 Page 43 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.227	-0.214	-0.237		
[95% CI]	[-0.277, -0.176]	[-0.266, -0.161]	[-0.308, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.086, 0.059] 0.724
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.076, 0.098] 0.808
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.112, 0.064] 0.595
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.267	-0.244	-0.235		
[95% CI]	[-0.320, -0.213]	[-0.299, -0.188]	[-0.311, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.023 [-0.100, 0.054] 0.560
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.031 [-0.124, 0.062] 0.510
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.086, 0.102] 0.865

Produced: 17 December 2020 Page 44 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.633	
Inter-Visit Period				0.175	
Treatment*Inter-Visit Period				0.340	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.164	-0.120	-0.174		
[95% CI]	[-0.207, -0.121]	[-0.165, -0.076]	[-0.233, -0.114]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.105, 0.018] 0.165
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.064, 0.083] 0.793
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.128, 0.021] 0.158

Produced: 17 December 2020 Page 45 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.232	-0.193	-0.233		
[95% CI]	[-0.283, -0.181]	[-0.246, -0.141]	[-0.304, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.112, 0.034] 0.298
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.087, 0.088] 0.994
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.128, 0.050] 0.386
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.274	-0.249	-0.270		
[95% CI]	[-0.329, -0.219]	[-0.306, -0.192]	[-0.348, -0.192]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.105, 0.055] 0.536
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.099, 0.092] 0.937
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.118, 0.076] 0.666

Produced: 17 December 2020 Page 46 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.292	-0.277	-0.261		
[95% CI]	[-0.352, -0.231]	[-0.340, -0.214]	[-0.346, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.102, 0.072] 0.741
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.031 [-0.136, 0.073] 0.559
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.016 [-0.090, 0.123] 0.760
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.321	-0.272	-0.247		
[95% CI]	[-0.384, -0.259]	[-0.337, -0.207]	[-0.335, -0.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.049 [-0.139, 0.040] 0.280
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.075 [-0.183, 0.033] 0.174
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.084, 0.135] 0.649

Produced: 17 December 2020 Page 47 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.244	-0.212	-0.244		
[95% CI]	[-0.293, -0.195]	[-0.263, -0.161]	[-0.313, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.103, 0.038] 0.371
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.085, 0.084] 0.992
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.117, 0.054] 0.466
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.275	-0.243	-0.249		
[95% CI]	[-0.328, -0.222]	[-0.298, -0.189]	[-0.323, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.107, 0.044] 0.416
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.117, 0.065] 0.577
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.098, 0.087] 0.905

Produced: 17 December 2020 Page 48 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: >=30					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.939	
Inter-Visit Period				0.360	
Treatment*Inter-Visit Period				0.878	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.096	-0.106	-0.105		
[95% CI]	[-0.129, -0.062]	[-0.140, -0.072]	[-0.152, -0.057]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.038, 0.058] 0.674
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.050, 0.067] 0.766
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.057, 0.060] 0.963

Produced: 17 December 2020 Page 49 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.147	-0.157	-0.151		
[95% CI]	[-0.189, -0.104]	[-0.199, -0.114]	[-0.211, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.050, 0.070] 0.742
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.069, 0.078] 0.901
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.068, 0.079] 0.884
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.180	-0.172	-0.179		
[95% CI]	[-0.228, -0.132]	[-0.220, -0.123]	[-0.247, -0.112]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.077, 0.060] 0.802
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.084, 0.082] 0.984
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.091, 0.075] 0.853

Produced: 17 December 2020 Page 50 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.188	-0.174	-0.211		
[95% CI]	[-0.240, -0.135]	[-0.227, -0.121]	[-0.286, -0.137]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.089, 0.061] 0.713
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.067, 0.115] 0.609
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.129, 0.054] 0.417
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.172	-0.158	-0.185		
[95% CI]	[-0.227, -0.116]	[-0.214, -0.103]	[-0.262, -0.107]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.092, 0.065] 0.731
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.082, 0.108] 0.790
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.122, 0.069] 0.583

Produced: 17 December 2020 Page 51 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.157	-0.157	-0.159		
[95% CI]	[-0.199, -0.115]	[-0.199, -0.115]	[-0.218, -0.100]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.059, 0.059] 0.999
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.070, 0.075] 0.950
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.075, 0.070] 0.949
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.169	-0.162	-0.179		
[95% CI]	[-0.214, -0.123]	[-0.208, -0.116]	[-0.244, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.072, 0.058] 0.833
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.068, 0.089] 0.793
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.097, 0.062] 0.664

Produced: 17 December 2020 Page 52 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.931	
Inter-Visit Period				0.611	
Treatment*Inter-Visit Period				0.566	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.110	-0.130	-0.101		
[95% CI]	[-0.150, -0.069]	[-0.170, -0.089]	[-0.158, -0.044]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.020 [-0.037, 0.077] 0.494
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.079, 0.061] 0.800
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.029 [-0.041, 0.099] 0.417

Produced: 17 December 2020 Page 53 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.174	-0.199	-0.162		
[95% CI]	[-0.224, -0.125]	[-0.248, -0.149]	[-0.232, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.024 [-0.046, 0.094] 0.495
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-0.098, 0.073] 0.776
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.037 [-0.049, 0.122] 0.400
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.237	-0.226	-0.210		
[95% CI]	[-0.293, -0.181]	[-0.282, -0.170]	[-0.289, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.090, 0.069] 0.789
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.123, 0.071] 0.595
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.082, 0.112] 0.755

Produced: 17 December 2020 Page 54 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.258	-0.226	-0.256		
[95% CI]	[-0.319, -0.198]	[-0.286, -0.165]	[-0.341, -0.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.118, 0.053] 0.456
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.003 [-0.107, 0.102] 0.962
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.135, 0.075] 0.573
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.243	-0.208	-0.215		
[95% CI]	[-0.306, -0.179]	[-0.272, -0.145]	[-0.304, -0.126]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.124, 0.055] 0.451
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.137, 0.081] 0.615
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.116, 0.103] 0.906

Produced: 17 December 2020 Page 55 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.198	-0.203	-0.179		
[95% CI]	[-0.246, -0.150]	[-0.251, -0.155]	[-0.246, -0.111]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.063, 0.072] 0.891
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.019 [-0.102, 0.063] 0.646
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.059, 0.107] 0.569
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.225	-0.210	-0.208		
[95% CI]	[-0.276, -0.173]	[-0.262, -0.158]	[-0.280, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.087, 0.059] 0.699
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.017 [-0.106, 0.072] 0.711
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.087, 0.092] 0.958

Produced: 17 December 2020 Page 56 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.988	
Inter-Visit Period				0.164	
Treatment*Inter-Visit Period				0.869	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.113	-0.122	-0.113		
[95% CI]	[-0.151, -0.075]	[-0.160, -0.084]	[-0.167, -0.059]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.045, 0.063] 0.747
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.066, 0.066] 0.993
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.057, 0.075] 0.785

Produced: 17 December 2020 Page 57 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.173	-0.190	-0.159		
[95% CI]	[-0.222, -0.125]	[-0.239, -0.142]	[-0.228, -0.091]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.017 [-0.052, 0.085] 0.633
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.098, 0.069] 0.740
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.031 [-0.053, 0.115] 0.470
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.201	-0.200	-0.190		
[95% CI]	[-0.254, -0.147]	[-0.254, -0.146]	[-0.266, -0.114]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.077, 0.076] 0.990
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.104, 0.082] 0.820
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.010 [-0.083, 0.103] 0.828

Produced: 17 December 2020 Page 58 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.204	-0.198	-0.222		
[95% CI]	[-0.264, -0.145]	[-0.258, -0.139]	[-0.305, -0.138]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.006 [-0.090, 0.078] 0.888
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.085, 0.120] 0.742
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.126, 0.079] 0.657
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.180	-0.188	-0.203		
[95% CI]	[-0.243, -0.117]	[-0.251, -0.125]	[-0.291, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.081, 0.097] 0.864
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.085, 0.131] 0.675
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.124, 0.093] 0.781

Produced: 17 December 2020 Page 59 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.179	-0.185	-0.169		
[95% CI]	[-0.225, -0.132]	[-0.232, -0.138]	[-0.234, -0.103]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.060, 0.072] 0.853
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.091, 0.070] 0.804
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.016 [-0.064, 0.097] 0.689
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.186	-0.189	-0.191		
[95% CI]	[-0.237, -0.135]	[-0.240, -0.138]	[-0.263, -0.119]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.069, 0.075] 0.929
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.083, 0.093] 0.914
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.090, 0.087] 0.972

Produced: 17 December 2020 Page 60 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.572	
Inter-Visit Period				0.056	
Treatment*Inter-Visit Period				0.978	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.068	-0.076	-0.103		
[95% CI]	[-0.108, -0.029]	[-0.116, -0.037]	[-0.159, -0.048]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.048, 0.064] 0.774
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.033, 0.104] 0.310
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.095, 0.041] 0.436

Produced: 17 December 2020 Page 61 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.104	-0.100	-0.131		
[95% CI]	[-0.151, -0.057]	[-0.147, -0.053]	[-0.197, -0.064]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.071, 0.063] 0.907
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.055, 0.108] 0.518
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.112, 0.051] 0.458
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.118	-0.123	-0.162		
[95% CI]	[-0.171, -0.064]	[-0.176, -0.069]	[-0.238, -0.087]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.071, 0.081] 0.897
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.045 [-0.048, 0.137] 0.342
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.132, 0.053] 0.399

Produced: 17 December 2020 Page 62 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.116	-0.128	-0.178		
[95% CI]	[-0.175, -0.056]	[-0.188, -0.069]	[-0.262, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.071, 0.097] 0.765
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.063 [-0.040, 0.165] 0.229
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.050 [-0.153, 0.053] 0.339
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.097	-0.105	-0.141		
[95% CI]	[-0.159, -0.035]	[-0.167, -0.044]	[-0.228, -0.055]		
p-value	0.002**	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.079, 0.096] 0.849
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.044 [-0.062, 0.150] 0.415
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.142, 0.071] 0.510

Produced: 17 December 2020 Page 63 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.106	-0.108	-0.144		
[95% CI]	[-0.152, -0.059]	[-0.155, -0.062]	[-0.209, -0.078]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.063, 0.069] 0.935
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [-0.043, 0.118] 0.357
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.116, 0.046] 0.393
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.106	-0.113	-0.152		
[95% CI]	[-0.158, -0.055]	[-0.164, -0.062]	[-0.224, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.066, 0.079] 0.855
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.046 [-0.042, 0.134] 0.307
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.128, 0.049] 0.384

Produced: 17 December 2020 Page 64 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.718	
Inter-Visit Period				0.257	
Treatment*Inter-Visit Period				0.680	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.091	-0.094	-0.102		
[95% CI]	[-0.132, -0.050]	[-0.135, -0.053]	[-0.160, -0.044]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.055, 0.061] 0.920
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.060, 0.082] 0.762
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.079, 0.063] 0.825

Produced: 17 December 2020 Page 65 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.136	-0.136	-0.155		
[95% CI]	[-0.185, -0.087]	[-0.185, -0.086]	[-0.225, -0.086]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.070, 0.069] 0.992
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.065, 0.104] 0.652
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.105, 0.065] 0.647
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.168	-0.135	-0.157		
[95% CI]	[-0.224, -0.112]	[-0.192, -0.079]	[-0.236, -0.078]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.112, 0.047] 0.421
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.107, 0.086] 0.830
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.119, 0.075] 0.656

Produced: 17 December 2020 Page 66 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.174	-0.140	-0.194		
[95% CI]	[-0.234, -0.113]	[-0.200, -0.079]	[-0.279, -0.109]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.119, 0.051] 0.434
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.084, 0.124] 0.706
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.158, 0.050] 0.308
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.171	-0.128	-0.184		
[95% CI]	[-0.234, -0.108]	[-0.191, -0.065]	[-0.273, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.043 [-0.132, 0.047] 0.348
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.096, 0.122] 0.814
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.165, 0.053] 0.315

Produced: 17 December 2020 Page 67 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.146	-0.129	-0.148		
[95% CI]	[-0.195, -0.098]	[-0.178, -0.080]	[-0.217, -0.079]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.086, 0.052] 0.625
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.082, 0.086] 0.964
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.104, 0.065] 0.656
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.159	-0.132	-0.169		
[95% CI]	[-0.212, -0.107]	[-0.184, -0.079]	[-0.242, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.028 [-0.102, 0.046] 0.464
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.081, 0.100] 0.839
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.037 [-0.128, 0.054] 0.422

Produced: 17 December 2020 Page 68 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	204	202	102		
Effect					
Treatment				0.971	
Inter-Visit Period				0.189	
Treatment*Inter-Visit Period				0.993	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.114	-0.125	-0.099		
[95% CI]	[-0.157, -0.072]	[-0.168, -0.082]	[-0.159, -0.038]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.050, 0.071] 0.734
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.090, 0.058] 0.677
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.026 [-0.048, 0.100] 0.488

Produced: 17 December 2020 Page 69 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.189	-0.193	-0.171		
[95% CI]	[-0.242, -0.136]	[-0.247, -0.140]	[-0.246, -0.097]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.070, 0.080] 0.903
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.109, 0.074] 0.707
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.022 [-0.070, 0.114] 0.635
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.210	-0.219	-0.210		
[95% CI]	[-0.268, -0.153]	[-0.277, -0.161]	[-0.292, -0.129]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.074, 0.090] 0.844
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.100, 0.100] 0.995
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.092, 0.109] 0.867

Produced: 17 December 2020 Page 70 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.220	-0.230	-0.243		
[95% CI]	[-0.283, -0.158]	[-0.293, -0.167]	[-0.331, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.079, 0.098] 0.830
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.086, 0.130] 0.685
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.121, 0.096] 0.819
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.199	-0.209	-0.217		
[95% CI]	[-0.263, -0.135]	[-0.273, -0.144]	[-0.307, -0.128]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.081, 0.100] 0.832
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.092, 0.129] 0.742
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.119, 0.102] 0.876

Produced: 17 December 2020 Page 71 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12c Statistical Analysis of Average Daily Asthma Symptoms score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.189	-0.196	-0.181		
[95% CI]	[-0.240, -0.138]	[-0.248, -0.145]	[-0.253, -0.109]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.065, 0.080] 0.840
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.097, 0.081] 0.860
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.073, 0.104] 0.733
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.200	-0.208	-0.206		
[95% CI]	[-0.254, -0.145]	[-0.263, -0.154]	[-0.283, -0.129]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.069, 0.086] 0.827
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.088, 0.100] 0.895
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.092, 0.096] 0.962

Produced: 17 December 2020 Page 72 of 72

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	488	489	245		
Effect					
Treatment				0.717	
Inter-Visit Period				0.222	
Treatment*Inter-Visit Period				0.597	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.126	-0.128	-0.126		
[95% CI]	[-0.150, -0.103]	[-0.151, -0.104]	[-0.159, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.032, 0.035] 0.934
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.041, 0.040] 0.970
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.039, 0.043] 0.917

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.185	-0.180	-0.174		
[95% CI]	[-0.213, -0.156]	[-0.209, -0.152]	[-0.214, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.045, 0.036] 0.835
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.060, 0.039] 0.672
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.006 [-0.043, 0.056] 0.801
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.223	-0.206	-0.213		
[95% CI]	[-0.255, -0.191]	[-0.238, -0.174]	[-0.258, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.062, 0.029] 0.473
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.065, 0.045] 0.719
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.062, 0.049] 0.821

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.242	-0.218	-0.226		
[95% CI]	[-0.276, -0.207]	[-0.253, -0.183]	[-0.275, -0.177]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.073, 0.025] 0.340
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.076, 0.044] 0.606
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.068, 0.052] 0.792
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.254	-0.223	-0.215		
[95% CI]	[-0.290, -0.218]	[-0.259, -0.187]	[-0.265, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.082, 0.019] 0.223
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.040 [-0.102, 0.023] 0.211
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.054, 0.070] 0.798

Produced: 17 December 2020

Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.196	-0.186	-0.187		
[95% CI]	[-0.224, -0.168]	[-0.214, -0.158]	[-0.227, -0.148]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.050, 0.030] 0.621
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.057, 0.040] 0.720
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.050, 0.047] 0.963
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.222	-0.203	-0.204		
[95% CI]	[-0.252, -0.192]	[-0.233, -0.173]	[-0.247, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.062, 0.024] 0.392
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.070, 0.035] 0.505
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.053, 0.052] 0.974

Produced: 17 December 2020 Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	488	489	245		
Effect					
Treatment				0.415	
Inter-Visit Period				0.168	
Treatment*Inter-Visit Period				0.357	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.140	-0.149	-0.116		
[95% CI]	[-0.167, -0.113]	[-0.176, -0.122]	[-0.155, -0.078]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.029, 0.047] 0.646
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.071, 0.023] 0.318
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.033 [-0.014, 0.080] 0.169

Produced: 17 December 2020 Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.205	-0.213	-0.177		
[95% CI]	[-0.238, -0.172]	[-0.246, -0.180]	[-0.224, -0.130]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.038, 0.055] 0.729
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.085, 0.029] 0.341
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.036 [-0.021, 0.093] 0.217
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.261	-0.248	-0.233		
[95% CI]	[-0.297, -0.224]	[-0.284, -0.212]	[-0.284, -0.181]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.064, 0.039] 0.629
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.091, 0.035] 0.384
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.048, 0.078] 0.635

Produced: 17 December 2020 Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.282	-0.261	-0.250		
[95% CI]	[-0.320, -0.244]	[-0.299, -0.222]	[-0.305, -0.196]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.076, 0.033] 0.446
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.099, 0.035] 0.349
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.056, 0.077] 0.753
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.301	-0.261	-0.232		
[95% CI]	[-0.341, -0.261]	[-0.300, -0.221]	[-0.288, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.096, 0.016] 0.161
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.069 [-0.138, -0.000] 0.050*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.029 [-0.040, 0.098] 0.412

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.225	-0.222	-0.198		
[95% CI]	[-0.256, -0.194]	[-0.253, -0.191]	[-0.242, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.047, 0.041] 0.898
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.027 [-0.082, 0.027] 0.325
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.030, 0.079] 0.379
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.258	-0.241	-0.220		
[95% CI]	[-0.291, -0.225]	[-0.275, -0.208]	[-0.267, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.063, 0.031] 0.493
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.038 [-0.096, 0.019] 0.194
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.022 [-0.036, 0.079] 0.459

Produced: 17 December 2020

Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	488	489	245		
Effect					
Treatment				0.923	
Inter-Visit Period				0.277	
Treatment*Inter-Visit Period				0.736	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.136	-0.145	-0.149		
[95% CI]	[-0.163, -0.109]	[-0.172, -0.119]	[-0.187, -0.111]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.028, 0.048] 0.623
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.033, 0.060] 0.575
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.050, 0.043] 0.873

Produced: 17 December 2020 Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.195	-0.208	-0.204		
[95% CI]	[-0.227, -0.163]	[-0.240, -0.175]	[-0.249, -0.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.033, 0.058] 0.585
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.047, 0.065] 0.757
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.052, 0.060] 0.891
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.222	-0.231	-0.241		
[95% CI]	[-0.258, -0.187]	[-0.266, -0.196]	[-0.291, -0.191]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.041, 0.059] 0.728
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.043, 0.080] 0.551
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.071, 0.052] 0.755

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.241	-0.234	-0.259		
[95% CI]	[-0.280, -0.203]	[-0.273, -0.196]	[-0.313, -0.204]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.061, 0.048] 0.805
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.049, 0.084] 0.605
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.091, 0.042] 0.473
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.253	-0.239	-0.249		
[95% CI]	[-0.293, -0.213]	[-0.279, -0.200]	[-0.305, -0.193]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.070, 0.042] 0.634
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.073, 0.065] 0.908
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.078, 0.059] 0.785

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.200	-0.211	-0.215		
[95% CI]	[-0.232, -0.169]	[-0.242, -0.180]	[-0.259, -0.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.034, 0.054] 0.651
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.039, 0.069] 0.591
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.059, 0.049] 0.866
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.224	-0.224	-0.235		
[95% CI]	[-0.257, -0.190]	[-0.257, -0.190]	[-0.282, -0.187]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.000 [-0.047, 0.047] 0.997
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.047, 0.069] 0.705
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.069, 0.047] 0.707

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	488	489	245		
Effect					
Treatment				0.766	
Inter-Visit Period				0.067	
Treatment*Inter-Visit Period				0.416	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.099	-0.097	-0.111		
[95% CI]	[-0.126, -0.072]	[-0.124, -0.070]	[-0.149, -0.073]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.040, 0.037] 0.931
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.035, 0.059] 0.617
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.061, 0.033] 0.568

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.150	-0.130	-0.140		
[95% CI]	[-0.181, -0.118]	[-0.162, -0.099]	[-0.185, -0.096]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.064, 0.025] 0.395
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.064, 0.046] 0.741
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.065, 0.045] 0.716
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.180	-0.160	-0.162		
[95% CI]	[-0.215, -0.144]	[-0.195, -0.125]	[-0.212, -0.112]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.069, 0.030] 0.445
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.079, 0.043] 0.568
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.063, 0.059] 0.958

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.190	-0.175	-0.171		
[95% CI]	[-0.228, -0.151]	[-0.213, -0.136]	[-0.226, -0.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.069, 0.039] 0.588
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.019 [-0.085, 0.048] 0.586
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.063, 0.070] 0.918
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.199	-0.183	-0.152		
[95% CI]	[-0.239, -0.159]	[-0.222, -0.143]	[-0.208, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.073, 0.040] 0.565
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.047 [-0.116, 0.021] 0.177
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.031 [-0.038, 0.100] 0.377

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.158	-0.141	-0.147		
[95% CI]	[-0.189, -0.127]	[-0.172, -0.110]	[-0.191, -0.104]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.061, 0.027] 0.456
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.064, 0.043] 0.700
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.060, 0.048] 0.823
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.176	-0.160	-0.155		
[95% CI]	[-0.210, -0.142]	[-0.193, -0.126]	[-0.202, -0.107]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.064, 0.031] 0.504
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.079, 0.037] 0.474
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.053, 0.063] 0.865

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	488	489	245		
Effect					
Treatment				0.240	
Inter-Visit Period				0.007**	
Treatment*Inter-Visit Period				0.532	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.130	-0.118	-0.126		
[95% CI]	[-0.158, -0.103]	[-0.146, -0.091]	[-0.165, -0.087]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.051, 0.027] 0.545
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.052, 0.043] 0.859
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.055, 0.040] 0.751

Produced: 17 December 2020 Page 17 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates
 [2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.190	-0.169	-0.174		
[95% CI]	[-0.223, -0.157]	[-0.202, -0.136]	[-0.221, -0.128]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.067, 0.026] 0.387
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.073, 0.042] 0.601
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.063, 0.052] 0.854
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.230	-0.184	-0.215		
[95% CI]	[-0.267, -0.194]	[-0.221, -0.148]	[-0.267, -0.163]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.046 [-0.098, 0.006] 0.083
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.079, 0.048] 0.631
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.094, 0.033] 0.350

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.257	-0.201	-0.225		
[95% CI]	[-0.297, -0.217]	[-0.240, -0.161]	[-0.281, -0.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.113, -0.000] 0.049*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.101, 0.036] 0.355
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.093, 0.045] 0.493
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.268	-0.206	-0.227		
[95% CI]	[-0.309, -0.226]	[-0.248, -0.165]	[-0.285, -0.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.061 [-0.120, -0.003] 0.040*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.041 [-0.113, 0.031] 0.262
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.092, 0.051] 0.578

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.203	-0.170	-0.189		
[95% CI]	[-0.235, -0.170]	[-0.202, -0.137]	[-0.234, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.079, 0.013] 0.157
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.070, 0.042] 0.629
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.075, 0.037] 0.501
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.232	-0.186	-0.207		
[95% CI]	[-0.267, -0.198]	[-0.221, -0.152]	[-0.256, -0.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.046 [-0.095, 0.003] 0.067
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.025 [-0.085, 0.035] 0.414
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.081, 0.039] 0.498

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	488	488	245		
Effect					
Treatment				0.510	
Inter-Visit Period				0.057	
Treatment*Inter-Visit Period				0.977	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.144	-0.127	-0.120		
[95% CI]	[-0.172, -0.115]	[-0.156, -0.099]	[-0.161, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.057, 0.024] 0.417
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.072, 0.026] 0.352
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.007 [-0.042, 0.056] 0.790

Produced: 17 December 2020 Page 21 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.217	-0.191	-0.189		
[95% CI]	[-0.251, -0.183]	[-0.225, -0.157]	[-0.237, -0.142]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.074, 0.022] 0.289
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.027 [-0.086, 0.031] 0.363
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.057, 0.060] 0.964
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.254	-0.227	-0.232		
[95% CI]	[-0.291, -0.217]	[-0.264, -0.190]	[-0.284, -0.179]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.079, 0.026] 0.320
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.022 [-0.086, 0.042] 0.501
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.069, 0.060] 0.889

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.268	-0.247	-0.245		
[95% CI]	[-0.308, -0.228]	[-0.288, -0.207]	[-0.302, -0.189]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.078, 0.036] 0.474
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.092, 0.047] 0.522
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.068, 0.072] 0.955
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.277	-0.243	-0.246		
[95% CI]	[-0.318, -0.236]	[-0.284, -0.202]	[-0.305, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.093, 0.024] 0.247
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.031 [-0.102, 0.041] 0.399
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.075, 0.068] 0.920

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.225	-0.201	-0.202		
[95% CI]	[-0.258, -0.193]	[-0.233, -0.168]	[-0.248, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.071, 0.022] 0.294
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.081, 0.033] 0.411
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.058, 0.056] 0.972
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.249	-0.223	-0.224		
[95% CI]	[-0.284, -0.214]	[-0.258, -0.188]	[-0.273, -0.174]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.075, 0.024] 0.304
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.025 [-0.086, 0.036] 0.416
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.061, 0.060] 0.979

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.138	
Inter-Visit Period				0.014*	
Treatment*Inter-Visit Period				0.978	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.076	-0.070	-0.210		
[95% CI]	[-0.133, -0.019]	[-0.128, -0.011]	[-0.290, -0.130]		
p-value	0.009**	0.020*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.088, 0.075] 0.874
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.134 [0.036, 0.232] 0.008**
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.141 [-0.240, -0.041] 0.006**

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.115	-0.096	-0.239		
[95% CI]	[-0.186, -0.045]	[-0.169, -0.023]	[-0.339, -0.139]		
p-value	0.002**	0.010*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.121, 0.082] 0.703
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.123 [0.001, 0.246] 0.049*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.143 [-0.267, -0.019] 0.024*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.137	-0.126	-0.241		
[95% CI]	[-0.216, -0.058]	[-0.207, -0.045]	[-0.352, -0.129]		
p-value	<0.001***	0.002**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.124, 0.103] 0.853
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.104 [-0.033, 0.241] 0.135
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.115 [-0.252, 0.023] 0.102

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.139	-0.141	-0.236		
[95% CI]	[-0.223, -0.054]	[-0.227, -0.055]	[-0.355, -0.117]		
p-value	0.001**	0.001**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.118, 0.123] 0.966
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.097 [-0.049, 0.243] 0.190
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.095 [-0.242, 0.052] 0.206
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.118	-0.103	-0.188		
[95% CI]	[-0.209, -0.027]	[-0.197, -0.010]	[-0.318, -0.059]		
p-value	0.012**	0.030*	0.005**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.145, 0.116] 0.825
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.070 [-0.088, 0.229] 0.383
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.085 [-0.245, 0.075] 0.296

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.121	-0.108	-0.235		
[95% CI]	[-0.190, -0.052]	[-0.179, -0.037]	[-0.332, -0.138]		
p-value	<0.001***	0.003**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.112, 0.086] 0.799
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.114 [-0.005, 0.234] 0.060
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.127 [-0.248, -0.007] 0.038*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.125	-0.116	-0.225		
[95% CI]	[-0.200, -0.050]	[-0.192, -0.039]	[-0.330, -0.119]		
p-value	0.001**	0.003**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.116, 0.098] 0.867
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.100 [-0.030, 0.229] 0.130
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.109 [-0.239, 0.022] 0.101

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.266	
Inter-Visit Period				0.062	
Treatment*Inter-Visit Period				0.971	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.002**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.087	-0.073	-0.208		
[95% CI]	[-0.154, -0.019]	[-0.143, -0.004]	[-0.304, -0.113]		
p-value	0.013*	0.039*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.110, 0.084] 0.790
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.122 [0.005, 0.239] 0.042*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.135 [-0.253, -0.017] 0.026*

Produced: 17 December 2020 Page 29 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.155	-0.122	-0.254		
[95% CI]	[-0.238, -0.071]	[-0.207, -0.036]	[-0.372, -0.137]		
p-value	<0.001***	0.006**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.153, 0.087] 0.586
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.099 [-0.045, 0.244] 0.176
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.133 [-0.278, 0.013] 0.074
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.177	-0.137	-0.257		
[95% CI]	[-0.268, -0.087]	[-0.230, -0.045]	[-0.384, -0.130]		
p-value	<0.001***	0.004**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.169, 0.089] 0.542
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.079 [-0.077, 0.235] 0.317
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.119 [-0.276, 0.038] 0.136

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.194	-0.153	-0.253		
[95% CI]	[-0.292, -0.097]	[-0.252, -0.053]	[-0.391, -0.115]		
p-value	<0.001***	0.003**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.181, 0.098] 0.557
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.059 [-0.110, 0.228] 0.495
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.100 [-0.271, 0.070] 0.248
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.176	-0.109	-0.188		
[95% CI]	[-0.281, -0.070]	[-0.217, -0.001]	[-0.337, -0.038]		
p-value	0.001**	0.047*	0.014*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.067 [-0.217, 0.084] 0.385
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.171, 0.195] 0.898
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.079 [-0.263, 0.106] 0.402

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.156	-0.123	-0.248		
[95% CI]	[-0.235, -0.078]	[-0.203, -0.042]	[-0.359, -0.138]		
p-value	<0.001***	0.003**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.146, 0.079] 0.554
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.092 [-0.044, 0.228] 0.182
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.126 [-0.263, 0.011] 0.071
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.171	-0.128	-0.236		
[95% CI]	[-0.256, -0.086]	[-0.214, -0.041]	[-0.355, -0.116]		
p-value	<0.001***	0.004**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.043 [-0.165, 0.078] 0.480
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.065 [-0.082, 0.211] 0.386
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.108 [-0.255, 0.040] 0.150

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.231	
Inter-Visit Period				0.054	
Treatment*Inter-Visit Period				0.822	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.132	-0.077	-0.256		
[95% CI]	[-0.197, -0.067]	[-0.144, -0.011]	[-0.348, -0.165]		
p-value	<0.001***	0.023*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.147, 0.038] 0.247
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.124 [0.013, 0.236] 0.029*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.179 [-0.292, -0.066] 0.002**

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.164	-0.109	-0.268		
[95% CI]	[-0.242, -0.085]	[-0.190, -0.029]	[-0.379, -0.157]		
p-value	<0.001***	0.008**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.167, 0.058] 0.340
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.104 [-0.031, 0.240] 0.131
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.159 [-0.296, -0.022] 0.023*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.192	-0.155	-0.239		
[95% CI]	[-0.280, -0.104]	[-0.245, -0.066]	[-0.362, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.162, 0.089] 0.568
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.105, 0.199] 0.543
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.083 [-0.236, 0.070] 0.284

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.185	-0.174	-0.253		
[95% CI]	[-0.278, -0.091]	[-0.270, -0.079]	[-0.386, -0.120]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.144, 0.123] 0.878
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.068 [-0.094, 0.231] 0.408
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.079 [-0.242, 0.085] 0.345
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.156	-0.132	-0.204		
[95% CI]	[-0.260, -0.052]	[-0.238, -0.026]	[-0.351, -0.056]		
p-value	0.003**	0.015*	0.007**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.173, 0.125] 0.751
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.134, 0.228] 0.607
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.071 [-0.253, 0.111] 0.441

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.174	-0.129	-0.250		
[95% CI]	[-0.250, -0.098]	[-0.207, -0.052]	[-0.357, -0.144]		
p-value	<0.001***	0.001**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.153, 0.063] 0.415
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.077 [-0.054, 0.207] 0.250
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.121 [-0.253, 0.010] 0.071
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.173	-0.142	-0.240		
[95% CI]	[-0.255, -0.091]	[-0.226, -0.058]	[-0.356, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.148, 0.086] 0.605
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.068 [-0.074, 0.209] 0.348
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.098 [-0.241, 0.044] 0.176

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.145	
Inter-Visit Period				0.064	
Treatment*Inter-Visit Period				0.966	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.019	-0.053	-0.144		
[95% CI]	[-0.084, 0.047]	[-0.120, 0.014]	[-0.237, -0.052]		
p-value	0.577	0.121	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					0.035 [-0.059, 0.128] 0.469
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.126 [0.013, 0.239] 0.030*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.091 [-0.205, 0.023] 0.117

Produced: 17 December 2020 Page 37 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.049	-0.067	-0.182		
[95% CI]	[-0.129, 0.030]	[-0.148, 0.015]	[-0.294, -0.070]		
p-value	0.225	0.109	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					0.018 [-0.097, 0.132] 0.762
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.133 [-0.005, 0.270] 0.059
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.115 [-0.254, 0.024] 0.103
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.057	-0.094	-0.209		
[95% CI]	[-0.146, 0.033]	[-0.185, -0.002]	[-0.335, -0.083]		
p-value	0.215	0.045*	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.037 [-0.091, 0.165] 0.567
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.152 [-0.002, 0.307] 0.053
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.115 [-0.271, 0.041] 0.147

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.063	-0.115	-0.200		
[95% CI]	[-0.160, 0.034]	[-0.214, -0.016]	[-0.337, -0.063]		
p-value	0.203	0.023*	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					0.052 [-0.087, 0.190] 0.460
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.137 [-0.031, 0.305] 0.109
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.085 [-0.254, 0.084] 0.322
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.045	-0.071	-0.169		
[95% CI]	[-0.148, 0.058]	[-0.177, 0.034]	[-0.316, -0.023]		
p-value	0.391	0.183	0.023*		
CHF 5993 pMDI - CHF 1535 pMDI					0.026 [-0.121, 0.174] 0.725
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.125 [-0.055, 0.304] 0.172
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.098 [-0.278, 0.082] 0.284

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.048	-0.079	-0.191		
[95% CI]	[-0.126, 0.029]	[-0.159, 0.000]	[-0.300, -0.082]		
p-value	0.219	0.050	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.031 [-0.080, 0.142] 0.584
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.142 [0.009, 0.276] 0.037*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.111 [-0.246, 0.023] 0.104
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.052	-0.087	-0.188		
[95% CI]	[-0.136, 0.033]	[-0.173, -0.000]	[-0.307, -0.069]		
p-value	0.231	0.049*	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					0.035 [-0.085, 0.156] 0.564
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.137 [-0.009, 0.283] 0.066
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.101 [-0.249, 0.046] 0.177

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.095	
Inter-Visit Period				0.004**	
Treatment*Inter-Visit Period				0.990	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.064	-0.077	-0.232		
[95% CI]	[-0.127, -0.002]	[-0.142, -0.013]	[-0.320, -0.143]		
p-value	0.044*	0.019*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.077, 0.103] 0.775
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.167 [0.059, 0.276] 0.003**
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.154 [-0.264, -0.045] 0.006**

Produced: 17 December 2020 Page 41 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.091	-0.086	-0.254		
[95% CI]	[-0.171, -0.011]	[-0.168, -0.004]	[-0.366, -0.141]		
p-value	0.026*	0.039*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.119, 0.110] 0.937
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.163 [0.025, 0.301] 0.021*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.167 [-0.307, -0.028] 0.019*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.118	-0.117	-0.261		
[95% CI]	[-0.208, -0.027]	[-0.210, -0.024]	[-0.389, -0.133]		
p-value	0.012*	0.014*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.130, 0.130] 0.998
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.144 [-0.013, 0.301] 0.073
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.144 [-0.302, 0.015] 0.075

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.110	-0.124	-0.239		
[95% CI]	[-0.209, -0.012]	[-0.225, -0.023]	[-0.379, -0.100]		
p-value	0.029*	0.017*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.128, 0.155] 0.849
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.129 [-0.042, 0.300] 0.138
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.116 [-0.288, 0.057] 0.189
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.092	-0.101	-0.195		
[95% CI]	[-0.195, 0.012]	[-0.207, 0.004]	[-0.341, -0.048]		
p-value	0.082	0.060	0.010**		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.138, 0.157] 0.897
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.103 [-0.076, 0.283] 0.259
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.093 [-0.274, 0.088] 0.310

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.101	-0.102	-0.254		
[95% CI]	[-0.180, -0.023]	[-0.182, -0.021]	[-0.365, -0.144]		
p-value	0.012*	0.014*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.112, 0.113] 0.993
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.153 [0.017, 0.289] 0.027*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.153 [-0.290, -0.015] 0.029*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.101	-0.108	-0.237		
[95% CI]	[-0.187, -0.016]	[-0.195, -0.020]	[-0.357, -0.116]		
p-value	0.020*	0.016*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.116, 0.129] 0.921
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.135 [-0.013, 0.283] 0.073
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.129 [-0.278, 0.020] 0.090

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.115	
Inter-Visit Period				0.139	
Treatment*Inter-Visit Period				0.557	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.002**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.107	-0.040	-0.221		
[95% CI]	[-0.175, -0.038]	[-0.110, 0.031]	[-0.318, -0.124]		
p-value	0.002**	0.271	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.067 [-0.166, 0.031] 0.180
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.114 [-0.004, 0.233] 0.059
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.181 [-0.302, -0.061] 0.003**

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.135	-0.071	-0.245		
[95% CI]	[-0.218, -0.051]	[-0.157, 0.016]	[-0.364, -0.127]		
p-value	0.002**	0.108	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.064 [-0.184, 0.056] 0.294
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.110 [-0.034, 0.255] 0.134
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.175 [-0.322, -0.027] 0.020*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.129	-0.114	-0.275		
[95% CI]	[-0.218, -0.040]	[-0.205, -0.023]	[-0.400, -0.149]		
p-value	0.005**	0.014*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.142, 0.113] 0.819
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.146 [-0.008, 0.299] 0.062
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.161 [-0.317, -0.005] 0.044*

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.142	-0.123	-0.251		
[95% CI]	[-0.238, -0.047]	[-0.222, -0.025]	[-0.387, -0.115]		
p-value	0.004**	0.014*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.157, 0.118] 0.783
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.109 [-0.058, 0.275] 0.199
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.128 [-0.297, 0.041] 0.137
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.131	-0.091	-0.176		
[95% CI]	[-0.234, -0.028]	[-0.196, 0.015]	[-0.323, -0.030]		
p-value	0.013*	0.092	0.018*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.188, 0.107] 0.589
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.045 [-0.133, 0.224] 0.616
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.086 [-0.267, 0.095] 0.351

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12d Statistical Analysis of Average Daily Asthma Symptoms score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.127	-0.089	-0.257		
[95% CI]	[-0.206, -0.049]	[-0.170, -0.008]	[-0.369, -0.146]		
p-value	0.002**	0.031*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.151, 0.075] 0.507
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.130 [-0.006, 0.266] 0.060
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.168 [-0.306, -0.030] 0.017*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.132	-0.099	-0.237		
[95% CI]	[-0.217, -0.048]	[-0.185, -0.012]	[-0.357, -0.117]		
p-value	0.002**	0.026*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.155, 0.088] 0.586
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.105 [-0.041, 0.251] 0.159
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.138 [-0.287, 0.010] 0.068

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	439	448	229		
Effect					
Treatment				0.936	
Inter-Visit Period				0.163	
Treatment*Inter-Visit Period				0.711	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.114	-0.123	-0.114		
[95% CI]	[-0.138, -0.090]	[-0.147, -0.100]	[-0.147, -0.081]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.024, 0.043] 0.592
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.040, 0.041] 0.992
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.031, 0.049] 0.664

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.159	-0.162	-0.157		
[95% CI]	[-0.188, -0.130]	[-0.191, -0.133]	[-0.197, -0.116]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.039, 0.043] 0.907
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.003 [-0.053, 0.047] 0.915
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.044, 0.055] 0.838
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.191	-0.183	-0.189		
[95% CI]	[-0.224, -0.158]	[-0.215, -0.150]	[-0.235, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.054, 0.038] 0.730
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.058, 0.054] 0.947
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.062, 0.050] 0.826

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.210	-0.199	-0.203		
[95% CI]	[-0.245, -0.174]	[-0.234, -0.163]	[-0.252, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.061, 0.039] 0.675
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.068, 0.054] 0.826
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.065, 0.057] 0.900
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.215	-0.197	-0.182		
[95% CI]	[-0.253, -0.178]	[-0.234, -0.160]	[-0.234, -0.130]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.071, 0.035] 0.504
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.033 [-0.097, 0.031] 0.318
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.049, 0.079] 0.651

Produced: 17 December 2020

Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.169	-0.167	-0.168		
[95% CI]	[-0.198, -0.141]	[-0.196, -0.139]	[-0.207, -0.128]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.043, 0.038] 0.914
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.051, 0.047] 0.942
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.000 [-0.049, 0.049] 0.987
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.191	-0.183	-0.180		
[95% CI]	[-0.222, -0.159]	[-0.214, -0.152]	[-0.224, -0.137]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.052, 0.036] 0.716
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.064, 0.043] 0.705
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.051, 0.055] 0.937

Produced: 17 December 2020

Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	439	448	229		
Effect					
Treatment				0.504	
Inter-Visit Period				0.032*	
Treatment*Inter-Visit Period				0.649	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.130	-0.137	-0.104		
[95% CI]	[-0.158, -0.102]	[-0.165, -0.110]	[-0.142, -0.066]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.032, 0.046] 0.717
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.073, 0.021] 0.278
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.033 [-0.014, 0.080] 0.165

Produced: 17 December 2020 Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.184	-0.187	-0.156		
[95% CI]	[-0.218, -0.150]	[-0.221, -0.153]	[-0.204, -0.109]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.046, 0.051] 0.912
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.086, 0.031] 0.357
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.030 [-0.028, 0.089] 0.310
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.224	-0.213	-0.201		
[95% CI]	[-0.263, -0.186]	[-0.251, -0.176]	[-0.254, -0.148]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.065, 0.043] 0.688
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.089, 0.042] 0.479
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.013 [-0.052, 0.077] 0.705

Produced: 17 December 2020

Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.245	-0.233	-0.221		
[95% CI]	[-0.285, -0.204]	[-0.273, -0.193]	[-0.277, -0.165]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.068, 0.045] 0.693
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.093, 0.046] 0.504
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.057, 0.081] 0.730
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.253	-0.231	-0.190		
[95% CI]	[-0.295, -0.210]	[-0.273, -0.189]	[-0.249, -0.131]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.022 [-0.082, 0.038] 0.471
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.062 [-0.135, 0.010] 0.092
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.041 [-0.032, 0.113] 0.272

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.197	-0.193	-0.172		
[95% CI]	[-0.230, -0.165]	[-0.226, -0.161]	[-0.218, -0.127]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.050, 0.042] 0.866
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.025 [-0.082, 0.031] 0.380
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.021 [-0.035, 0.077] 0.458
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.223	-0.213	-0.190		
[95% CI]	[-0.258, -0.188]	[-0.248, -0.178]	[-0.238, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.059, 0.039] 0.687
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.033 [-0.093, 0.027] 0.275
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.023 [-0.037, 0.083] 0.446

Produced: 17 December 2020 Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	439	448	229		
Effect					
Treatment				0.788	
Inter-Visit Period				0.140	
Treatment*Inter-Visit Period				0.903	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.130	-0.142	-0.139		
[95% CI]	[-0.157, -0.103]	[-0.169, -0.115]	[-0.176, -0.101]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.026, 0.051] 0.535
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.038, 0.055] 0.720
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.043, 0.050] 0.878

Produced: 17 December 2020

Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.169	-0.189	-0.190		
[95% CI]	[-0.202, -0.136]	[-0.222, -0.156]	[-0.236, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.020 [-0.026, 0.067] 0.390
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.035, 0.078] 0.449
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.058, 0.055] 0.961
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.190	-0.211	-0.218		
[95% CI]	[-0.227, -0.154]	[-0.247, -0.174]	[-0.268, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.020 [-0.031, 0.072] 0.436
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.028 [-0.035, 0.090] 0.385
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.069, 0.055] 0.820

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.211	-0.220	-0.233		
[95% CI]	[-0.251, -0.172]	[-0.260, -0.181]	[-0.289, -0.178]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.047, 0.065] 0.757
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.046, 0.090] 0.529
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.081, 0.055] 0.707
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.213	-0.218	-0.214		
[95% CI]	[-0.255, -0.172]	[-0.259, -0.177]	[-0.272, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.053, 0.064] 0.866
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.070, 0.072] 0.974
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.067, 0.075] 0.915

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.174	-0.193	-0.197		
[95% CI]	[-0.206, -0.142]	[-0.225, -0.162]	[-0.241, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.026, 0.064] 0.404
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.032, 0.077] 0.411
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.058, 0.051] 0.892
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.193	-0.206	-0.211		
[95% CI]	[-0.228, -0.159]	[-0.241, -0.172]	[-0.259, -0.163]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.035, 0.062] 0.596
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.041, 0.077] 0.558
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.063, 0.054] 0.881

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	439	448	229		
Effect					
Treatment				0.986	
Inter-Visit Period				0.059	
Treatment*Inter-Visit Period				0.388	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.078	-0.103	-0.098		
[95% CI]	[-0.105, -0.050]	[-0.130, -0.075]	[-0.137, -0.060]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.025 [-0.014, 0.064] 0.209
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.027, 0.068] 0.394
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.043, 0.052] 0.854

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.122	-0.121	-0.123		
[95% CI]	[-0.155, -0.089]	[-0.153, -0.088]	[-0.169, -0.078]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.048, 0.045] 0.957
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.055, 0.058] 0.954
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.059, 0.053] 0.918
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.149	-0.142	-0.147		
[95% CI]	[-0.186, -0.112]	[-0.178, -0.105]	[-0.198, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.060, 0.045] 0.778
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.003 [-0.066, 0.061] 0.933
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.068, 0.058] 0.882

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.159	-0.161	-0.158		
[95% CI]	[-0.199, -0.119]	[-0.201, -0.121]	[-0.214, -0.102]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.055, 0.059] 0.942
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.070, 0.068] 0.984
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.066, 0.072] 0.935
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.164	-0.158	-0.134		
[95% CI]	[-0.206, -0.122]	[-0.199, -0.116]	[-0.192, -0.076]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.006 [-0.065, 0.053] 0.839
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.030 [-0.101, 0.042] 0.417
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.048, 0.095] 0.519

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.130	-0.129	-0.132		
[95% CI]	[-0.162, -0.097]	[-0.161, -0.097]	[-0.177, -0.087]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.046, 0.045] 0.980
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.053, 0.058] 0.938
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.058, 0.053] 0.921
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.145	-0.144	-0.140		
[95% CI]	[-0.181, -0.110]	[-0.179, -0.109]	[-0.188, -0.091]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.051, 0.048] 0.964
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.066, 0.054] 0.847
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.055, 0.065] 0.876

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	439	448	229		
Effect					
Treatment				0.435	
Inter-Visit Period				0.007**	
Treatment*Inter-Visit Period				0.625	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.118	-0.110	-0.117		
[95% CI]	[-0.145, -0.090]	[-0.138, -0.083]	[-0.156, -0.079]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.047, 0.032] 0.705
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.048, 0.047] 0.992
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.055, 0.040] 0.762

Produced: 17 December 2020 Page 17 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.163	-0.150	-0.157		
[95% CI]	[-0.197, -0.129]	[-0.184, -0.117]	[-0.204, -0.110]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.060, 0.035] 0.610
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.063, 0.053] 0.856
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.065, 0.051] 0.811
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.201	-0.165	-0.193		
[95% CI]	[-0.239, -0.163]	[-0.202, -0.127]	[-0.245, -0.140]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.090, 0.017] 0.183
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.073, 0.056] 0.801
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.092, 0.037] 0.397

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.225	-0.179	-0.201		
[95% CI]	[-0.266, -0.184]	[-0.220, -0.139]	[-0.258, -0.144]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.103, 0.013] 0.125
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.094, 0.047] 0.513
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.092, 0.048] 0.542
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.233	-0.180	-0.194		
[95% CI]	[-0.276, -0.190]	[-0.223, -0.138]	[-0.254, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.053 [-0.113, 0.008] 0.087
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.039 [-0.112, 0.035] 0.303
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.088, 0.059] 0.706

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.176	-0.152	-0.170		
[95% CI]	[-0.210, -0.143]	[-0.185, -0.119]	[-0.216, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.071, 0.022] 0.305
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.063, 0.051] 0.831
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.075, 0.038] 0.526
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.202	-0.166	-0.184		
[95% CI]	[-0.238, -0.167]	[-0.201, -0.130]	[-0.234, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.087, 0.014] 0.155
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.080, 0.043] 0.557
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.079, 0.043] 0.558

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	439	447	229		
Effect					
Treatment				0.873	
Inter-Visit Period				0.070	
Treatment*Inter-Visit Period				0.843	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.127	-0.112	-0.108		
[95% CI]	[-0.157, -0.098]	[-0.141, -0.083]	[-0.148, -0.067]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.057, 0.026] 0.470
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.020 [-0.070, 0.031] 0.442
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.046, 0.055] 0.861

Produced: 17 December 2020 Page 21 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.184	-0.164	-0.171		
[95% CI]	[-0.219, -0.148]	[-0.199, -0.129]	[-0.220, -0.122]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.069, 0.030] 0.445
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-0.073, 0.048] 0.689
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.067, 0.053] 0.818
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.208	-0.199	-0.209		
[95% CI]	[-0.247, -0.169]	[-0.237, -0.160]	[-0.263, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.064, 0.046] 0.747
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.066, 0.068] 0.974
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.077, 0.056] 0.765

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.220	-0.221	-0.214		
[95% CI]	[-0.262, -0.178]	[-0.263, -0.179]	[-0.273, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.059, 0.060] 0.985
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.078, 0.066] 0.871
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.007 [-0.066, 0.079] 0.859
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.225	-0.212	-0.199		
[95% CI]	[-0.269, -0.182]	[-0.256, -0.169]	[-0.260, -0.139]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.075, 0.048] 0.677
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.101, 0.049] 0.499
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.013 [-0.062, 0.087] 0.737

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.188	-0.175	-0.182		
[95% CI]	[-0.222, -0.153]	[-0.209, -0.141]	[-0.230, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.062, 0.035] 0.594
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.065, 0.053] 0.835
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.066, 0.052] 0.817
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.205	-0.196	-0.195		
[95% CI]	[-0.242, -0.168]	[-0.232, -0.159]	[-0.246, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.061, 0.042] 0.721
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.074, 0.052] 0.739
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.062, 0.064] 0.969

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.272	
Inter-Visit Period				0.101	
Treatment*Inter-Visit Period				0.955	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.140	-0.107	-0.222		
[95% CI]	[-0.192, -0.089]	[-0.160, -0.053]	[-0.300, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.108, 0.040] 0.371
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.082 [-0.011, 0.175] 0.085
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.115 [-0.210, -0.021] 0.016*

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.232	-0.192	-0.275		
[95% CI]	[-0.292, -0.172]	[-0.255, -0.129]	[-0.366, -0.184]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.127, 0.047] 0.371
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.043 [-0.066, 0.153] 0.438
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.083 [-0.194, 0.028] 0.142
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.281	-0.239	-0.310		
[95% CI]	[-0.347, -0.216]	[-0.307, -0.171]	[-0.409, -0.211]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.137, 0.052] 0.379
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.029 [-0.090, 0.147] 0.636
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.071 [-0.191, 0.049] 0.246

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates
 [2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.292	-0.237	-0.308		
[95% CI]	[-0.363, -0.221]	[-0.311, -0.163]	[-0.416, -0.201]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.158, 0.048] 0.292
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.113, 0.145] 0.808
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.071 [-0.202, 0.060] 0.285
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.307	-0.238	-0.307		
[95% CI]	[-0.381, -0.234]	[-0.315, -0.161]	[-0.419, -0.196]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.070 [-0.176, 0.037] 0.200
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.134, 0.134] 0.999
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.070 [-0.205, 0.066] 0.312

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.245	-0.204	-0.286		
[95% CI]	[-0.302, -0.187]	[-0.265, -0.144]	[-0.373, -0.199]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.123, 0.043] 0.344
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.041 [-0.063, 0.146] 0.439
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.081 [-0.187, 0.025] 0.132
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.272	-0.221	-0.297		
[95% CI]	[-0.334, -0.210]	[-0.286, -0.156]	[-0.391, -0.203]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.051 [-0.141, 0.039] 0.265
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.088, 0.138] 0.664
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.076 [-0.190, 0.038] 0.192

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.391	
Inter-Visit Period				0.376	
Treatment*Inter-Visit Period				0.304	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.146	-0.143	-0.222		
[95% CI]	[-0.205, -0.087]	[-0.204, -0.081]	[-0.311, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.089, 0.082] 0.934
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.076 [-0.030, 0.183] 0.160
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.080 [-0.188, 0.028] 0.146

Produced: 17 December 2020 Page 29 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.249	-0.248	-0.302		
[95% CI]	[-0.316, -0.181]	[-0.318, -0.177]	[-0.404, -0.200]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.099, 0.097] 0.984
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.053 [-0.070, 0.176] 0.396
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.178, 0.070] 0.392
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.337	-0.301	-0.362		
[95% CI]	[-0.408, -0.266]	[-0.375, -0.227]	[-0.469, -0.255]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.138, 0.067] 0.497
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.104, 0.154] 0.701
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.191, 0.070] 0.360

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.360	-0.288	-0.352		
[95% CI]	[-0.437, -0.284]	[-0.368, -0.208]	[-0.467, -0.236]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.184, 0.038] 0.198
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.147, 0.130] 0.902
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.204, 0.076] 0.370
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.394	-0.268	-0.355		
[95% CI]	[-0.472, -0.315]	[-0.350, -0.186]	[-0.473, -0.237]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.125 [-0.239, -0.012] 0.030*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.039 [-0.181, 0.103] 0.590
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.087 [-0.230, 0.057] 0.236

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.280	-0.260	-0.322		
[95% CI]	[-0.342, -0.219]	[-0.325, -0.196]	[-0.415, -0.229]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.109, 0.069] 0.660
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.042 [-0.070, 0.154] 0.465
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.062 [-0.175, 0.052] 0.285
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.328	-0.270	-0.338		
[95% CI]	[-0.393, -0.263]	[-0.338, -0.201]	[-0.436, -0.239]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.153, 0.036] 0.223
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.109, 0.128] 0.875
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.068 [-0.188, 0.052] 0.264

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.240	
Inter-Visit Period				0.109	
Treatment*Inter-Visit Period				0.622	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.156	-0.113	-0.261		
[95% CI]	[-0.213, -0.099]	[-0.173, -0.053]	[-0.348, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.043 [-0.126, 0.040] 0.310
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.105 [0.002, 0.209] 0.046*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.148 [-0.253, -0.043] 0.006**

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.268	-0.212	-0.287		
[95% CI]	[-0.335, -0.200]	[-0.283, -0.142]	[-0.390, -0.185]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.056 [-0.153, 0.042] 0.264
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.104, 0.142] 0.759
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.075 [-0.199, 0.050] 0.238
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.315	-0.257	-0.314		
[95% CI]	[-0.388, -0.242]	[-0.334, -0.181]	[-0.425, -0.203]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.163, 0.048] 0.286
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.134, 0.132] 0.988
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.191, 0.078] 0.410

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.310	-0.246	-0.335		
[95% CI]	[-0.389, -0.232]	[-0.328, -0.165]	[-0.453, -0.216]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.064 [-0.177, 0.049] 0.267
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.118, 0.166] 0.737
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.088 [-0.232, 0.056] 0.228
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.332	-0.247	-0.334		
[95% CI]	[-0.412, -0.251]	[-0.331, -0.163]	[-0.456, -0.212]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.085 [-0.201, 0.032] 0.154
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.144, 0.149] 0.975
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.087 [-0.235, 0.061] 0.250

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.276	-0.221	-0.297		
[95% CI]	[-0.340, -0.212]	[-0.288, -0.154]	[-0.395, -0.200]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.148, 0.038] 0.249
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.095, 0.139] 0.716
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.076 [-0.195, 0.042] 0.206
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.298	-0.234	-0.316		
[95% CI]	[-0.367, -0.230]	[-0.306, -0.162]	[-0.420, -0.212]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.064 [-0.163, 0.035] 0.204
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.107, 0.142] 0.778
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.082 [-0.208, 0.044] 0.202

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.477	
Inter-Visit Period				0.118	
Treatment*Inter-Visit Period				0.802	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.123	-0.050	-0.176		
[95% CI]	[-0.180, -0.066]	[-0.109, 0.010]	[-0.262, -0.090]		
p-value	<0.001***	0.103	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.156, 0.009] 0.080
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.053 [-0.051, 0.156] 0.317
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.126 [-0.231, -0.021] 0.018*

Produced: 17 December 2020 Page 37 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.184	-0.126	-0.223		
[95% CI]	[-0.248, -0.120]	[-0.193, -0.059]	[-0.320, -0.126]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.058 [-0.151, 0.034] 0.215
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.039 [-0.078, 0.155] 0.515
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.097 [-0.215, 0.021] 0.107
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.209	-0.186	-0.241		
[95% CI]	[-0.279, -0.138]	[-0.260, -0.113]	[-0.347, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.022 [-0.123, 0.079] 0.669
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.032 [-0.096, 0.160] 0.623
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.183, 0.075] 0.412

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.218	-0.189	-0.228		
[95% CI]	[-0.296, -0.141]	[-0.270, -0.108]	[-0.345, -0.110]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.030 [-0.142, 0.082] 0.603
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.132, 0.150] 0.897
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.182, 0.104] 0.592
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.225	-0.205	-0.218		
[95% CI]	[-0.305, -0.145]	[-0.289, -0.121]	[-0.340, -0.096]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.136, 0.096] 0.735
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.153, 0.139] 0.924
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.161, 0.135] 0.864

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.188	-0.147	-0.225		
[95% CI]	[-0.250, -0.126]	[-0.211, -0.082]	[-0.319, -0.131]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.131, 0.048] 0.365
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.037 [-0.075, 0.150] 0.516
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.078 [-0.192, 0.036] 0.177
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.205	-0.171	-0.224		
[95% CI]	[-0.272, -0.138]	[-0.242, -0.101]	[-0.326, -0.122]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.130, 0.064] 0.502
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.103, 0.142] 0.754
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.053 [-0.176, 0.071] 0.403

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.239	
Inter-Visit Period				0.050	
Treatment*Inter-Visit Period				0.993	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.135	-0.121	-0.231		
[95% CI]	[-0.193, -0.077]	[-0.181, -0.060]	[-0.318, -0.144]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.098, 0.069] 0.738
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.096 [-0.009, 0.200] 0.073
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.110 [-0.216, -0.004] 0.042*

Produced: 17 December 2020 Page 41 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.223	-0.183	-0.292		
[95% CI]	[-0.292, -0.154]	[-0.255, -0.110]	[-0.397, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.140, 0.060] 0.432
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.070 [-0.056, 0.195] 0.277
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.110 [-0.237, 0.018] 0.091
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.264	-0.212	-0.327		
[95% CI]	[-0.340, -0.188]	[-0.291, -0.132]	[-0.443, -0.212]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.052 [-0.162, 0.058] 0.354
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.064 [-0.075, 0.202] 0.365
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.116 [-0.256, 0.024] 0.105

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.278	-0.226	-0.321		
[95% CI]	[-0.359, -0.196]	[-0.312, -0.141]	[-0.444, -0.197]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.052 [-0.170, 0.067] 0.392
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.043 [-0.105, 0.191] 0.568
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.095 [-0.245, 0.055] 0.216
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.278	-0.232	-0.325		
[95% CI]	[-0.363, -0.193]	[-0.321, -0.143]	[-0.453, -0.196]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.046 [-0.169, 0.077] 0.466
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.107, 0.201] 0.550
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.093 [-0.249, 0.064] 0.244

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.231	-0.189	-0.302		
[95% CI]	[-0.298, -0.165]	[-0.258, -0.119]	[-0.402, -0.201]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.139, 0.054] 0.386
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.070 [-0.050, 0.191] 0.252
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.113 [-0.235, 0.009] 0.070
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.255	-0.209	-0.312		
[95% CI]	[-0.326, -0.183]	[-0.284, -0.134]	[-0.420, -0.204]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.046 [-0.149, 0.058] 0.386
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.058 [-0.072, 0.187] 0.383
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.103 [-0.235, 0.028] 0.123

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.126	
Inter-Visit Period				0.030*	
Treatment*Inter-Visit Period				0.920	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.178	-0.125	-0.238		
[95% CI]	[-0.235, -0.121]	[-0.185, -0.065]	[-0.324, -0.152]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.053 [-0.136, 0.030] 0.208
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.060 [-0.044, 0.164] 0.256
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.113 [-0.218, -0.008] 0.035*

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.281	-0.209	-0.290		
[95% CI]	[-0.348, -0.213]	[-0.279, -0.138]	[-0.392, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.072 [-0.170, 0.025] 0.145
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.114, 0.132] 0.885
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.081 [-0.206, 0.043] 0.199
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.335	-0.258	-0.341		
[95% CI]	[-0.406, -0.265]	[-0.331, -0.184]	[-0.448, -0.234]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.078 [-0.180, 0.025] 0.136
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.123, 0.134] 0.930
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.083 [-0.214, 0.047] 0.208

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.356	-0.264	-0.360		
[95% CI]	[-0.432, -0.280]	[-0.344, -0.184]	[-0.475, -0.244]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.092 [-0.203, 0.018] 0.102
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.135, 0.142] 0.959
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.096 [-0.236, 0.045] 0.180
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.366	-0.256	-0.371		
[95% CI]	[-0.444, -0.287]	[-0.338, -0.174]	[-0.490, -0.252]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.109 [-0.223, 0.005] 0.060
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.137, 0.149] 0.939
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.115 [-0.260, 0.030] 0.119

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12e Statistical Analysis of Average Daily Asthma Symptoms score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.294	-0.222	-0.309		
[95% CI]	[-0.357, -0.232]	[-0.288, -0.156]	[-0.404, -0.214]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.072 [-0.163, 0.018] 0.118
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.099, 0.129] 0.794
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.087 [-0.203, 0.028] 0.137
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.327	-0.241	-0.337		
[95% CI]	[-0.394, -0.261]	[-0.311, -0.171]	[-0.438, -0.236]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.183, 0.010] 0.080
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.112, 0.131] 0.873
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.096 [-0.219, 0.027] 0.125

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.818	
Inter-Visit Period				0.321	
Treatment*Inter-Visit Period				0.889	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.099	-0.099	-0.125		
[95% CI]	[-0.126, -0.071]	[-0.127, -0.071]	[-0.164, -0.086]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.000 [-0.039, 0.040] 0.992
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.021, 0.074] 0.272
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.075, 0.022] 0.281

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.155	-0.158	-0.167		
[95% CI]	[-0.189, -0.121]	[-0.193, -0.123]	[-0.215, -0.118]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.047, 0.051] 0.923
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.048, 0.071] 0.702
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.069, 0.051] 0.765
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.183	-0.175	-0.194		
[95% CI]	[-0.222, -0.144]	[-0.216, -0.135]	[-0.250, -0.138]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.064, 0.048] 0.780
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.058, 0.079] 0.760
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.088, 0.050] 0.596

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.198	-0.182	-0.197		
[95% CI]	[-0.241, -0.155]	[-0.227, -0.138]	[-0.258, -0.136]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.077, 0.046] 0.618
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.075, 0.074] 0.987
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.091, 0.061] 0.697
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.195	-0.165	-0.190		
[95% CI]	[-0.241, -0.150]	[-0.212, -0.118]	[-0.255, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.096, 0.035] 0.358
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.085, 0.074] 0.892
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.106, 0.055] 0.540

Produced: 17 December 2020

Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.162	-0.158	-0.175		
[95% CI]	[-0.195, -0.128]	[-0.193, -0.123]	[-0.223, -0.127]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.052, 0.045] 0.886
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.045, 0.072] 0.655
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.076, 0.043] 0.577
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.179	-0.166	-0.184		
[95% CI]	[-0.216, -0.142]	[-0.205, -0.127]	[-0.238, -0.131]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.067, 0.041] 0.634
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.060, 0.070] 0.874
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.084, 0.048] 0.586

Produced: 17 December 2020

Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.541	
Inter-Visit Period				0.056	
Treatment*Inter-Visit Period				0.478	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.113	-0.109	-0.105		
[95% CI]	[-0.146, -0.079]	[-0.144, -0.075]	[-0.152, -0.057]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.051, 0.045] 0.894
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.066, 0.050] 0.791
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.054, 0.063] 0.879

Produced: 17 December 2020

Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.186	-0.186	-0.159		
[95% CI]	[-0.227, -0.145]	[-0.229, -0.144]	[-0.217, -0.101]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.000 [-0.058, 0.059] 0.991
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.027 [-0.098, 0.044] 0.459
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.027 [-0.045, 0.099] 0.459
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.229	-0.200	-0.197		
[95% CI]	[-0.274, -0.184]	[-0.247, -0.153]	[-0.262, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.094, 0.037] 0.389
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.111, 0.047] 0.430
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.077, 0.083] 0.939

Produced: 17 December 2020

Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.243	-0.209	-0.208		
[95% CI]	[-0.292, -0.194]	[-0.260, -0.158]	[-0.279, -0.138]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.105, 0.037] 0.344
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.035 [-0.121, 0.051] 0.424
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.086, 0.088] 0.985
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.250	-0.185	-0.190		
[95% CI]	[-0.302, -0.199]	[-0.239, -0.132]	[-0.264, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.065 [-0.139, 0.010] 0.088
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.060 [-0.151, 0.030] 0.189
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.096, 0.087] 0.930

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.198	-0.182	-0.171		
[95% CI]	[-0.237, -0.159]	[-0.222, -0.142]	[-0.227, -0.116]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.072, 0.040] 0.578
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.027 [-0.094, 0.041] 0.440
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.058, 0.079] 0.758
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.222	-0.190	-0.185		
[95% CI]	[-0.264, -0.180]	[-0.234, -0.146]	[-0.246, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.093, 0.029] 0.301
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.037 [-0.110, 0.037] 0.328
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.070, 0.079] 0.902

Produced: 17 December 2020

Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.542	
Inter-Visit Period				0.163	
Treatment*Inter-Visit Period				0.959	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.117	-0.111	-0.171		
[95% CI]	[-0.149, -0.086]	[-0.144, -0.078]	[-0.217, -0.126]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.053, 0.039] 0.772
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.054 [-0.002, 0.109] 0.058
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.117, -0.004] 0.035*

Produced: 17 December 2020 Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.169	-0.178	-0.214		
[95% CI]	[-0.209, -0.130]	[-0.219, -0.138]	[-0.271, -0.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.048, 0.066] 0.755
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.045 [-0.024, 0.114] 0.200
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.106, 0.034] 0.312
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.198	-0.197	-0.225		
[95% CI]	[-0.241, -0.154]	[-0.242, -0.151]	[-0.287, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.064, 0.062] 0.974
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.049, 0.103] 0.483
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.105, 0.049] 0.472

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.211	-0.203	-0.229		
[95% CI]	[-0.259, -0.163]	[-0.252, -0.153]	[-0.297, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.077, 0.060] 0.815
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.065, 0.101] 0.670
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.111, 0.058] 0.541
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.204	-0.192	-0.223		
[95% CI]	[-0.255, -0.154]	[-0.245, -0.140]	[-0.296, -0.151]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.085, 0.061] 0.748
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.069, 0.107] 0.674
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.120, 0.059] 0.498

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.177	-0.178	-0.213		
[95% CI]	[-0.215, -0.139]	[-0.217, -0.138]	[-0.268, -0.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.053, 0.056] 0.966
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.037 [-0.029, 0.103] 0.277
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.103, 0.032] 0.298
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.192	-0.188	-0.220		
[95% CI]	[-0.234, -0.151]	[-0.231, -0.145]	[-0.279, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.064, 0.055] 0.886
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.028 [-0.045, 0.100] 0.455
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.105, 0.041] 0.393

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.591	
Inter-Visit Period				0.233	
Treatment*Inter-Visit Period				0.946	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.063	-0.074	-0.110		
[95% CI]	[-0.094, -0.032]	[-0.106, -0.042]	[-0.154, -0.065]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.034, 0.056] 0.633
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.008, 0.101] 0.094
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.091, 0.020] 0.205

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.112	-0.110	-0.141		
[95% CI]	[-0.150, -0.075]	[-0.149, -0.071]	[-0.195, -0.087]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.057, 0.051] 0.918
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.029 [-0.037, 0.094] 0.391
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.098, 0.035] 0.352
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.127	-0.134	-0.165		
[95% CI]	[-0.170, -0.084]	[-0.179, -0.090]	[-0.227, -0.103]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.055, 0.069] 0.819
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [-0.037, 0.113] 0.322
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.107, 0.045] 0.428

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.135	-0.140	-0.162		
[95% CI]	[-0.183, -0.087]	[-0.190, -0.091]	[-0.231, -0.093]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.064, 0.074] 0.879
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.056, 0.111] 0.523
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.106, 0.063] 0.613
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.131	-0.123	-0.155		
[95% CI]	[-0.182, -0.081]	[-0.175, -0.071]	[-0.227, -0.082]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.081, 0.064] 0.821
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.065, 0.111] 0.602
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.121, 0.057] 0.484

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.113	-0.117	-0.149		
[95% CI]	[-0.150, -0.076]	[-0.156, -0.079]	[-0.202, -0.096]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.049, 0.058] 0.862
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.036 [-0.028, 0.101] 0.269
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.097, 0.034] 0.342
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.123	-0.125	-0.154		
[95% CI]	[-0.164, -0.082]	[-0.168, -0.082]	[-0.213, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.057, 0.061] 0.951
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.041, 0.103] 0.398
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.029 [-0.102, 0.044] 0.433

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.819	
Inter-Visit Period				0.068	
Treatment*Inter-Visit Period				0.707	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.100	-0.100	-0.117		
[95% CI]	[-0.132, -0.067]	[-0.133, -0.066]	[-0.163, -0.070]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.000 [-0.047, 0.047] 0.992
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.040, 0.074] 0.555
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.074, 0.041] 0.565

Produced: 17 December 2020 Page 17 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.152	-0.155	-0.154		
[95% CI]	[-0.192, -0.113]	[-0.196, -0.114]	[-0.210, -0.097]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.055, 0.060] 0.929
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.068, 0.070] 0.974
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.069, 0.072] 0.968
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.180	-0.168	-0.189		
[95% CI]	[-0.225, -0.134]	[-0.215, -0.121]	[-0.254, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.077, 0.054] 0.732
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.070, 0.088] 0.817
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.101, 0.059] 0.612

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.204	-0.175	-0.191		
[95% CI]	[-0.254, -0.154]	[-0.227, -0.123]	[-0.263, -0.120]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.101, 0.043] 0.432
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.013 [-0.100, 0.075] 0.776
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.104, 0.072] 0.720
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.200	-0.157	-0.196		
[95% CI]	[-0.252, -0.147]	[-0.211, -0.102]	[-0.271, -0.120]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.043 [-0.119, 0.033] 0.265
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.096, 0.088] 0.928
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.132, 0.054] 0.414

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.159	-0.154	-0.167		
[95% CI]	[-0.198, -0.120]	[-0.194, -0.113]	[-0.223, -0.111]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.062, 0.051] 0.854
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.060, 0.076] 0.818
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.082, 0.056] 0.706
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.180	-0.160	-0.180		
[95% CI]	[-0.223, -0.137]	[-0.205, -0.116]	[-0.242, -0.118]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.082, 0.042] 0.520
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.076, 0.075] 0.992
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.096, 0.056] 0.607

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.511	
Inter-Visit Period				0.109	
Treatment*Inter-Visit Period				0.868	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.117	-0.091	-0.140		
[95% CI]	[-0.151, -0.083]	[-0.126, -0.056]	[-0.189, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.074, 0.023] 0.301
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.035, 0.082] 0.433
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.049 [-0.109, 0.010] 0.105

Produced: 17 December 2020 Page 21 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.191	-0.156	-0.179		
[95% CI]	[-0.232, -0.150]	[-0.198, -0.114]	[-0.237, -0.121]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.094, 0.024] 0.242
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-0.083, 0.059] 0.740
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.095, 0.049] 0.531
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.219	-0.186	-0.217		
[95% CI]	[-0.265, -0.174]	[-0.233, -0.139]	[-0.282, -0.152]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.098, 0.033] 0.326
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.082, 0.077] 0.956
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.111, 0.050] 0.456

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.226	-0.204	-0.226		
[95% CI]	[-0.276, -0.175]	[-0.256, -0.152]	[-0.298, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.022 [-0.094, 0.051] 0.556
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.087, 0.089] 0.984
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.111, 0.066] 0.618
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.222	-0.184	-0.223		
[95% CI]	[-0.274, -0.169]	[-0.239, -0.129]	[-0.299, -0.148]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.113, 0.038] 0.330
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.091, 0.094] 0.974
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.132, 0.054] 0.410

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.195	-0.162	-0.193		
[95% CI]	[-0.234, -0.155]	[-0.203, -0.121]	[-0.250, -0.137]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.089, 0.025] 0.266
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.070, 0.068] 0.971
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.101, 0.039] 0.384
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.209	-0.179	-0.209		
[95% CI]	[-0.253, -0.166]	[-0.224, -0.134]	[-0.271, -0.147]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.093, 0.032] 0.335
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.076, 0.076] 0.999
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.107, 0.046] 0.433

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.733	
Inter-Visit Period				0.013*	
Treatment*Inter-Visit Period				0.305	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.141	-0.140	-0.151		
[95% CI]	[-0.176, -0.107]	[-0.173, -0.107]	[-0.199, -0.104]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.049, 0.047] 0.962
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.049, 0.069] 0.735
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.070, 0.047] 0.703

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.197	-0.179	-0.201		
[95% CI]	[-0.238, -0.155]	[-0.219, -0.139]	[-0.258, -0.144]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.075, 0.039] 0.542
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.066, 0.075] 0.902
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.092, 0.048] 0.532
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.241	-0.214	-0.241		
[95% CI]	[-0.286, -0.196]	[-0.257, -0.170]	[-0.304, -0.178]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.090, 0.035] 0.395
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.077, 0.077] 0.998
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.103, 0.049] 0.486

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.260	-0.231	-0.260		
[95% CI]	[-0.308, -0.212]	[-0.278, -0.184]	[-0.327, -0.193]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.096, 0.038] 0.399
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.083, 0.083] 0.999
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.029 [-0.110, 0.053] 0.489
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.279	-0.245	-0.233		
[95% CI]	[-0.329, -0.230]	[-0.293, -0.197]	[-0.303, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.103, 0.035] 0.335
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.046 [-0.131, 0.039] 0.291
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.072, 0.096] 0.782

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.212	-0.192	-0.215		
[95% CI]	[-0.252, -0.172]	[-0.230, -0.153]	[-0.271, -0.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.076, 0.035] 0.475
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.066, 0.071] 0.934
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.091, 0.045] 0.503
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.240	-0.215	-0.231		
[95% CI]	[-0.283, -0.198]	[-0.256, -0.174]	[-0.290, -0.172]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.085, 0.033] 0.393
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.082, 0.064] 0.805
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.088, 0.055] 0.651

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.958	
Inter-Visit Period				0.047*	
Treatment*Inter-Visit Period				0.601	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.154	-0.167	-0.156		
[95% CI]	[-0.193, -0.116]	[-0.204, -0.130]	[-0.210, -0.103]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.041, 0.066] 0.641
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.064, 0.068] 0.956
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.054, 0.076] 0.743

Produced: 17 December 2020 Page 29 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.211	-0.214	-0.218		
[95% CI]	[-0.257, -0.164]	[-0.259, -0.169]	[-0.283, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.061, 0.069] 0.911
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.073, 0.087] 0.856
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.083, 0.075] 0.927
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.271	-0.264	-0.277		
[95% CI]	[-0.321, -0.221]	[-0.313, -0.215]	[-0.347, -0.207]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.077, 0.063] 0.844
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.080, 0.092] 0.893
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.098, 0.072] 0.766

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.299	-0.281	-0.295		
[95% CI]	[-0.352, -0.247]	[-0.332, -0.230]	[-0.369, -0.222]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.091, 0.055] 0.629
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.095, 0.086] 0.928
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.103, 0.076] 0.761
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.321	-0.291	-0.264		
[95% CI]	[-0.375, -0.266]	[-0.344, -0.239]	[-0.340, -0.189]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.030 [-0.105, 0.046] 0.443
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.056 [-0.150, 0.037] 0.236
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.027 [-0.065, 0.119] 0.569

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.234	-0.234	-0.240		
[95% CI]	[-0.279, -0.190]	[-0.276, -0.191]	[-0.302, -0.179]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.062, 0.061] 0.982
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.070, 0.081] 0.881
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.081, 0.068] 0.865
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.272	-0.260	-0.261		
[95% CI]	[-0.318, -0.226]	[-0.304, -0.215]	[-0.324, -0.197]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.076, 0.052] 0.711
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.090, 0.067] 0.779
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.079, 0.077] 0.984

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.943	
Inter-Visit Period				0.086	
Treatment*Inter-Visit Period				0.341	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.154	-0.160	-0.158		
[95% CI]	[-0.193, -0.115]	[-0.198, -0.123]	[-0.212, -0.105]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.047, 0.060] 0.815
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.062, 0.070] 0.897
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.063, 0.067] 0.951

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.214	-0.209	-0.212		
[95% CI]	[-0.260, -0.169]	[-0.253, -0.165]	[-0.275, -0.149]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.068, 0.058] 0.871
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.080, 0.076] 0.957
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.080, 0.074] 0.937
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.241	-0.244	-0.257		
[95% CI]	[-0.290, -0.191]	[-0.292, -0.196]	[-0.326, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.066, 0.072] 0.934
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.069, 0.101] 0.705
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.098, 0.071] 0.753

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.258	-0.249	-0.289		
[95% CI]	[-0.312, -0.205]	[-0.300, -0.197]	[-0.364, -0.214]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.084, 0.065] 0.795
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.061, 0.122] 0.514
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.131, 0.050] 0.383
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.279	-0.256	-0.264		
[95% CI]	[-0.334, -0.225]	[-0.309, -0.203]	[-0.340, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.100, 0.052] 0.543
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.109, 0.079] 0.750
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.101, 0.084] 0.860

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.219	-0.220	-0.228		
[95% CI]	[-0.263, -0.175]	[-0.263, -0.178]	[-0.289, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.060, 0.062] 0.976
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.066, 0.084] 0.817
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.082, 0.066] 0.834
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.244	-0.236	-0.253		
[95% CI]	[-0.290, -0.197]	[-0.281, -0.191]	[-0.317, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.072, 0.057] 0.817
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.070, 0.089] 0.822
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.095, 0.062] 0.676

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.718	
Inter-Visit Period				0.019*	
Treatment*Inter-Visit Period				0.077	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.114	-0.107	-0.123		
[95% CI]	[-0.154, -0.074]	[-0.146, -0.069]	[-0.178, -0.068]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.006 [-0.062, 0.049] 0.819
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.059, 0.077] 0.791
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.083, 0.052] 0.648

Produced: 17 December 2020 Page 37 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.162	-0.132	-0.153		
[95% CI]	[-0.208, -0.116]	[-0.176, -0.087]	[-0.218, -0.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.030 [-0.094, 0.034] 0.361
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.087, 0.071] 0.839
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.100, 0.056] 0.586
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.202	-0.166	-0.173		
[95% CI]	[-0.252, -0.152]	[-0.214, -0.118]	[-0.243, -0.104]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.105, 0.034] 0.312
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.114, 0.057] 0.515
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.092, 0.077] 0.864

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.213	-0.190	-0.191		
[95% CI]	[-0.267, -0.160]	[-0.242, -0.138]	[-0.266, -0.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.023 [-0.098, 0.052] 0.544
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.022 [-0.114, 0.070] 0.640
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.092, 0.090] 0.980
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.229	-0.208	-0.156		
[95% CI]	[-0.284, -0.174]	[-0.261, -0.155]	[-0.232, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.097, 0.055] 0.591
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.073 [-0.167, 0.021] 0.129
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.052 [-0.041, 0.145] 0.273

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.176	-0.146	-0.159		
[95% CI]	[-0.221, -0.131]	[-0.190, -0.103]	[-0.222, -0.097]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.092, 0.033] 0.352
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.093, 0.060] 0.674
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.089, 0.063] 0.735
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.198	-0.172	-0.167		
[95% CI]	[-0.246, -0.151]	[-0.218, -0.127]	[-0.233, -0.101]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.092, 0.040] 0.443
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.031 [-0.112, 0.050] 0.455
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.075, 0.085] 0.900

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.196	
Inter-Visit Period				0.005**	
Treatment*Inter-Visit Period				0.374	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.144	-0.125	-0.168		
[95% CI]	[-0.183, -0.105]	[-0.163, -0.087]	[-0.222, -0.114]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.073, 0.035] 0.499
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.043, 0.091] 0.476
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.043 [-0.109, 0.023] 0.202

Produced: 17 December 2020 Page 41 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.201	-0.160	-0.220		
[95% CI]	[-0.249, -0.154]	[-0.206, -0.115]	[-0.286, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.107, 0.024] 0.216
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.062, 0.100] 0.648
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.060 [-0.140, 0.020] 0.140
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.253	-0.182	-0.256		
[95% CI]	[-0.304, -0.201]	[-0.232, -0.132]	[-0.328, -0.185]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.071 [-0.142, 0.001] 0.052
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.085, 0.092] 0.940
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.074 [-0.161, 0.013] 0.095

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.271	-0.204	-0.265		
[95% CI]	[-0.326, -0.216]	[-0.257, -0.151]	[-0.342, -0.189]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.067 [-0.143, 0.009] 0.085
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.099, 0.089] 0.912
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.062 [-0.155, 0.031] 0.194
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.290	-0.226	-0.251		
[95% CI]	[-0.347, -0.234]	[-0.280, -0.171]	[-0.330, -0.172]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.065 [-0.143, 0.014] 0.107
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.039 [-0.136, 0.058] 0.427
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.121, 0.071] 0.604

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.220	-0.166	-0.232		
[95% CI]	[-0.266, -0.174]	[-0.211, -0.122]	[-0.295, -0.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.054 [-0.117, 0.010] 0.098
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.067, 0.090] 0.777
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.065 [-0.143, 0.012] 0.100
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.250	-0.190	-0.245		
[95% CI]	[-0.298, -0.202]	[-0.237, -0.143]	[-0.312, -0.178]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.127, 0.007] 0.081
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.088, 0.078] 0.909
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.055 [-0.137, 0.027] 0.188

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	271	289	140		
Effect					
Treatment				0.735	
Inter-Visit Period				0.031*	
Treatment*Inter-Visit Period				0.751	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.162	-0.138	-0.130		
[95% CI]	[-0.203, -0.121]	[-0.178, -0.099]	[-0.186, -0.073]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.080, 0.033] 0.410
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.102, 0.037] 0.361
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.060, 0.078] 0.806

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.220	-0.192	-0.217		
[95% CI]	[-0.268, -0.171]	[-0.239, -0.145]	[-0.284, -0.149]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.028 [-0.095, 0.040] 0.418
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.003 [-0.086, 0.080] 0.937
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.107, 0.058] 0.559
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.254	-0.236	-0.260		
[95% CI]	[-0.306, -0.202]	[-0.286, -0.186]	[-0.332, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.090, 0.054] 0.623
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.083, 0.095] 0.895
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.112, 0.064] 0.591

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.277	-0.256	-0.267		
[95% CI]	[-0.332, -0.222]	[-0.309, -0.202]	[-0.344, -0.190]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.098, 0.056] 0.592
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.104, 0.085] 0.843
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.105, 0.082] 0.811
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.294	-0.259	-0.250		
[95% CI]	[-0.350, -0.238]	[-0.313, -0.205]	[-0.328, -0.172]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.113, 0.043] 0.375
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.044 [-0.141, 0.052] 0.368
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.086, 0.104] 0.855

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12f Statistical Analysis of Average Daily Asthma Symptoms score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.229	-0.207	-0.227		
[95% CI]	[-0.276, -0.183]	[-0.253, -0.162]	[-0.291, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.022 [-0.087, 0.043] 0.506
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.003 [-0.083, 0.077] 0.945
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.098, 0.060] 0.634
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.257	-0.232	-0.243		
[95% CI]	[-0.306, -0.209]	[-0.279, -0.185]	[-0.311, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.093, 0.043] 0.472
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.098, 0.069] 0.738
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.093, 0.072] 0.801

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	129	137	74		
Effect					
Treatment				0.379	
Inter-Visit Period				0.159	
Treatment*Inter-Visit Period				0.993	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.154	-0.114	-0.178		
[95% CI]	[-0.202, -0.106]	[-0.161, -0.068]	[-0.242, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.107, 0.027] 0.242
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.056, 0.104] 0.557
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.143, 0.015] 0.112

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.193	-0.165	-0.228		
[95% CI]	[-0.249, -0.136]	[-0.220, -0.110]	[-0.303, -0.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.028 [-0.106, 0.051] 0.491
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.058, 0.129] 0.458
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.063 [-0.155, 0.029] 0.181
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.231	-0.191	-0.246		
[95% CI]	[-0.294, -0.167]	[-0.253, -0.130]	[-0.330, -0.163]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.128, 0.049] 0.380
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.089, 0.121] 0.768
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.055 [-0.159, 0.048] 0.296

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.241	-0.194	-0.257		
[95% CI]	[-0.313, -0.169]	[-0.264, -0.124]	[-0.353, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.148, 0.053] 0.354
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.103, 0.136] 0.789
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.182, 0.054] 0.289
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.255	-0.195	-0.256		
[95% CI]	[-0.333, -0.177]	[-0.271, -0.120]	[-0.359, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.168, 0.049] 0.283
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.128, 0.130] 0.987
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.060 [-0.188, 0.067] 0.351

Produced: 17 December 2020 Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.207	-0.171	-0.230		
[95% CI]	[-0.263, -0.151]	[-0.225, -0.117]	[-0.304, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.114, 0.042] 0.364
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.069, 0.116] 0.624
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.059 [-0.150, 0.032] 0.205
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.227	-0.183	-0.244		
[95% CI]	[-0.290, -0.165]	[-0.243, -0.123]	[-0.326, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.131, 0.042] 0.315
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.087, 0.119] 0.758
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.163, 0.041] 0.243

Produced: 17 December 2020 Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	129	137	74		
Effect					
Treatment				0.352	
Inter-Visit Period				0.325	
Treatment*Inter-Visit Period				0.970	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.170	-0.135	-0.192		
[95% CI]	[-0.225, -0.115]	[-0.188, -0.081]	[-0.265, -0.119]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.112, 0.042] 0.367
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.069, 0.114] 0.630
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.058 [-0.148, 0.033] 0.210

Produced: 17 December 2020 Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.222	-0.203	-0.261		
[95% CI]	[-0.287, -0.157]	[-0.266, -0.140]	[-0.347, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.109, 0.072] 0.691
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.039 [-0.069, 0.147] 0.478
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.057 [-0.164, 0.049] 0.292
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.275	-0.233	-0.314		
[95% CI]	[-0.346, -0.204]	[-0.302, -0.164]	[-0.408, -0.220]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.141, 0.057] 0.404
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.039 [-0.079, 0.158] 0.514
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.081 [-0.198, 0.035] 0.171

Produced: 17 December 2020

Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.288	-0.241	-0.313		
[95% CI]	[-0.367, -0.209]	[-0.318, -0.164]	[-0.418, -0.208]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.157, 0.063] 0.402
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.106, 0.157] 0.706
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.072 [-0.202, 0.058] 0.274
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.301	-0.227	-0.319		
[95% CI]	[-0.385, -0.216]	[-0.309, -0.145]	[-0.431, -0.207]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.191, 0.045] 0.223
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.122, 0.159] 0.797
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.092 [-0.231, 0.047] 0.195

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.242	-0.209	-0.279		
[95% CI]	[-0.304, -0.180]	[-0.269, -0.148]	[-0.361, -0.197]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.120, 0.053] 0.443
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.037 [-0.067, 0.140] 0.486
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.070 [-0.172, 0.031] 0.175
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.268	-0.222	-0.297		
[95% CI]	[-0.336, -0.200]	[-0.287, -0.156]	[-0.387, -0.208]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.046 [-0.141, 0.048] 0.333
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.029 [-0.083, 0.142] 0.608
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.076 [-0.187, 0.035] 0.180

Produced: 17 December 2020

Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	129	137	74		
Effect					
Treatment				0.484	
Inter-Visit Period				0.123	
Treatment*Inter-Visit Period				0.957	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.164	-0.125	-0.204		
[95% CI]	[-0.218, -0.110]	[-0.178, -0.073]	[-0.275, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.114, 0.037] 0.312
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.040 [-0.050, 0.129] 0.385
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.078 [-0.167, 0.010] 0.082

Produced: 17 December 2020

Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.200	-0.183	-0.246		
[95% CI]	[-0.263, -0.137]	[-0.244, -0.123]	[-0.328, -0.163]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.104, 0.071] 0.711
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.046 [-0.059, 0.150] 0.389
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.062 [-0.165, 0.041] 0.235
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.249	-0.216	-0.258		
[95% CI]	[-0.320, -0.179]	[-0.284, -0.148]	[-0.350, -0.165]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.131, 0.065] 0.509
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.108, 0.125] 0.888
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.041 [-0.156, 0.074] 0.481

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.264	-0.217	-0.274		
[95% CI]	[-0.344, -0.185]	[-0.295, -0.140]	[-0.380, -0.169]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.158, 0.064] 0.406
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.122, 0.142] 0.883
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.057 [-0.188, 0.074] 0.392
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.276	-0.225	-0.285		
[95% CI]	[-0.361, -0.192]	[-0.307, -0.143]	[-0.396, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.051 [-0.169, 0.067] 0.393
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.132, 0.149] 0.909
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.059 [-0.198, 0.079] 0.399

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates
 [2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.221	-0.192	-0.246		
[95% CI]	[-0.282, -0.160]	[-0.252, -0.133]	[-0.327, -0.165]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.114, 0.057] 0.509
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.077, 0.127] 0.634
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.053 [-0.154, 0.047] 0.296
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.245	-0.207	-0.262		
[95% CI]	[-0.314, -0.177]	[-0.273, -0.140]	[-0.352, -0.172]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.134, 0.056] 0.422
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.096, 0.130] 0.769
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.167, 0.056] 0.326

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	129	137	74		
Effect					
Treatment				0.672	
Inter-Visit Period				0.013*	
Treatment*Inter-Visit Period				0.449	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.114	-0.098	-0.155		
[95% CI]	[-0.165, -0.063]	[-0.147, -0.048]	[-0.222, -0.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.087, 0.055] 0.655
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.041 [-0.043, 0.125] 0.339
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.057 [-0.141, 0.026] 0.178

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.162	-0.127	-0.198		
[95% CI]	[-0.222, -0.102]	[-0.186, -0.069]	[-0.277, -0.118]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.118, 0.049] 0.415
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.064, 0.135] 0.483
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.070 [-0.169, 0.028] 0.161
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.182	-0.158	-0.181		
[95% CI]	[-0.249, -0.114]	[-0.223, -0.092]	[-0.270, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.118, 0.070] 0.618
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.113, 0.111] 0.990
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.134, 0.087] 0.681

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.182	-0.153	-0.199		
[95% CI]	[-0.259, -0.105]	[-0.227, -0.078]	[-0.301, -0.098]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.136, 0.078] 0.594
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.110, 0.144] 0.788
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.046 [-0.172, 0.079] 0.468
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.206	-0.162	-0.170		
[95% CI]	[-0.289, -0.123]	[-0.243, -0.082]	[-0.279, -0.060]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.160, 0.072] 0.455
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.037 [-0.174, 0.101] 0.600
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.143, 0.128] 0.916

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.165	-0.139	-0.182		
[95% CI]	[-0.224, -0.106]	[-0.196, -0.082]	[-0.260, -0.104]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.108, 0.056] 0.532
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.081, 0.114] 0.734
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.043 [-0.139, 0.053] 0.381
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.179	-0.148	-0.184		
[95% CI]	[-0.245, -0.113]	[-0.212, -0.084]	[-0.271, -0.097]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.123, 0.061] 0.509
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.105, 0.114] 0.934
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.144, 0.073] 0.517

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	129	137	74		
Effect					
Treatment				0.258	
Inter-Visit Period				0.061	
Treatment*Inter-Visit Period				0.978	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.169	-0.097	-0.163		
[95% CI]	[-0.225, -0.113]	[-0.152, -0.043]	[-0.236, -0.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.072 [-0.149, 0.006] 0.070
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.099, 0.086] 0.891
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.065 [-0.157, 0.026] 0.161

Produced: 17 December 2020 Page 17 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.187	-0.145	-0.211		
[95% CI]	[-0.252, -0.122]	[-0.208, -0.081]	[-0.298, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.133, 0.049] 0.363
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.084, 0.133] 0.655
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.067 [-0.174, 0.040] 0.221
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.217	-0.157	-0.238		
[95% CI]	[-0.290, -0.144]	[-0.227, -0.086]	[-0.334, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.162, 0.041] 0.244
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.100, 0.142] 0.735
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.081 [-0.201, 0.038] 0.183

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.230	-0.162	-0.248		
[95% CI]	[-0.310, -0.150]	[-0.239, -0.084]	[-0.354, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.068 [-0.180, 0.043] 0.228
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.114, 0.151] 0.787
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.087 [-0.218, 0.044] 0.194
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.236	-0.166	-0.254		
[95% CI]	[-0.322, -0.150]	[-0.249, -0.082]	[-0.368, -0.140]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.071 [-0.191, 0.049] 0.248
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.125, 0.160] 0.811
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.088 [-0.229, 0.053] 0.221

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.200	-0.144	-0.218		
[95% CI]	[-0.265, -0.136]	[-0.206, -0.081]	[-0.303, -0.133]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.056 [-0.146, 0.033] 0.216
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.089, 0.125] 0.743
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.074 [-0.180, 0.031] 0.167
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.217	-0.154	-0.234		
[95% CI]	[-0.287, -0.147]	[-0.222, -0.086]	[-0.327, -0.142]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.063 [-0.161, 0.035] 0.206
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.099, 0.134] 0.764
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.081 [-0.196, 0.034] 0.168

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	129	136	74		
Effect					
Treatment				0.333	
Inter-Visit Period				0.115	
Treatment*Inter-Visit Period				0.991	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.166	-0.106	-0.193		
[95% CI]	[-0.224, -0.107]	[-0.163, -0.049]	[-0.270, -0.116]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.141, 0.022] 0.152
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.070, 0.124] 0.580
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.087 [-0.183, 0.009] 0.076

Produced: 17 December 2020 Page 21 of 48
 Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.222	-0.152	-0.233		
[95% CI]	[-0.288, -0.155]	[-0.216, -0.087]	[-0.321, -0.146]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.070 [-0.162, 0.022] 0.137
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.099, 0.121] 0.839
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.081 [-0.190, 0.027] 0.141
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.253	-0.201	-0.260		
[95% CI]	[-0.324, -0.182]	[-0.270, -0.131]	[-0.354, -0.165]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.052 [-0.152, 0.047] 0.303
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.111, 0.125] 0.911
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.059 [-0.176, 0.058] 0.322

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.257	-0.216	-0.264		
[95% CI]	[-0.335, -0.179]	[-0.292, -0.140]	[-0.368, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.150, 0.068] 0.456
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.122, 0.137] 0.914
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.049 [-0.177, 0.080] 0.457
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.264	-0.207	-0.271		
[95% CI]	[-0.348, -0.181]	[-0.288, -0.125]	[-0.381, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.058 [-0.174, 0.059] 0.333
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.132, 0.145] 0.926
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.201, 0.073] 0.359

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.230	-0.171	-0.241		
[95% CI]	[-0.294, -0.166]	[-0.233, -0.109]	[-0.325, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.148, 0.030] 0.195
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.095, 0.117] 0.834
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.070 [-0.175, 0.034] 0.188
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.245	-0.191	-0.254		
[95% CI]	[-0.314, -0.177]	[-0.258, -0.125]	[-0.345, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.054 [-0.149, 0.042] 0.269
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.104, 0.123] 0.875
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.063 [-0.175, 0.049] 0.271

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.985	
Inter-Visit Period				0.095	
Treatment*Inter-Visit Period				0.505	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.108	-0.122	-0.126		
[95% CI]	[-0.132, -0.083]	[-0.147, -0.097]	[-0.161, -0.090]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.021, 0.049] 0.423
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.025, 0.061] 0.414
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.047, 0.039] 0.868

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.169	-0.170	-0.169		
[95% CI]	[-0.199, -0.138]	[-0.200, -0.139]	[-0.213, -0.126]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.042, 0.044] 0.957
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.052, 0.053] 0.981
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.052, 0.054] 0.984
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.204	-0.196	-0.208		
[95% CI]	[-0.237, -0.170]	[-0.230, -0.162]	[-0.256, -0.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.055, 0.040] 0.764
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.055, 0.063] 0.888
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.071, 0.048] 0.701

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.221	-0.212	-0.219		
[95% CI]	[-0.257, -0.186]	[-0.248, -0.176]	[-0.271, -0.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.061, 0.041] 0.709
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.065, 0.061] 0.952
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.071, 0.055] 0.810
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.227	-0.210	-0.198		
[95% CI]	[-0.264, -0.190]	[-0.247, -0.173]	[-0.252, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.070, 0.036] 0.525
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.029 [-0.094, 0.036] 0.386
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.054, 0.077] 0.725

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.178	-0.177	-0.183		
[95% CI]	[-0.207, -0.149]	[-0.206, -0.147]	[-0.226, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.043, 0.040] 0.948
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.046, 0.057] 0.843
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.058, 0.045] 0.802
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.201	-0.194	-0.196		
[95% CI]	[-0.233, -0.169]	[-0.226, -0.162]	[-0.242, -0.151]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.052, 0.038] 0.752
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.060, 0.051] 0.872
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.058, 0.053] 0.924

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.438	
Inter-Visit Period				0.014*	
Treatment*Inter-Visit Period				0.191	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.120	-0.140	-0.110		
[95% CI]	[-0.149, -0.092]	[-0.169, -0.112]	[-0.151, -0.069]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.020 [-0.020, 0.060] 0.333
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.060, 0.039] 0.684
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.030 [-0.020, 0.080] 0.235

Produced: 17 December 2020 Page 29 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.190	-0.199	-0.163		
[95% CI]	[-0.225, -0.155]	[-0.235, -0.164]	[-0.214, -0.113]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.041, 0.059] 0.721
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.027 [-0.088, 0.035] 0.395
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.036 [-0.026, 0.097] 0.256
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.241	-0.233	-0.210		
[95% CI]	[-0.279, -0.202]	[-0.271, -0.194]	[-0.265, -0.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.063, 0.047] 0.773
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.031 [-0.098, 0.036] 0.367
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.023 [-0.045, 0.091] 0.506

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.263	-0.247	-0.231		
[95% CI]	[-0.303, -0.223]	[-0.288, -0.207]	[-0.289, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.073, 0.042] 0.597
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.102, 0.039] 0.379
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.016 [-0.055, 0.087] 0.652
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.277	-0.244	-0.195		
[95% CI]	[-0.319, -0.236]	[-0.286, -0.202]	[-0.256, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-0.093, 0.025] 0.264
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.082 [-0.155, -0.009] 0.028*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.048 [-0.025, 0.122] 0.197

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.207	-0.208	-0.180		
[95% CI]	[-0.240, -0.173]	[-0.242, -0.174]	[-0.228, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.046, 0.049] 0.949
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.085, 0.032] 0.372
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.028 [-0.030, 0.086] 0.347
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.238	-0.227	-0.197		
[95% CI]	[-0.273, -0.203]	[-0.262, -0.192]	[-0.248, -0.147]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.061, 0.039] 0.660
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.041 [-0.102, 0.021] 0.193
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.030 [-0.032, 0.091] 0.347

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.778	
Inter-Visit Period				0.130	
Treatment*Inter-Visit Period				0.764	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.126	-0.140	-0.152		
[95% CI]	[-0.154, -0.098]	[-0.168, -0.111]	[-0.192, -0.112]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.027, 0.053] 0.514
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.026 [-0.024, 0.075] 0.308
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.062, 0.037] 0.625

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.187	-0.198	-0.202		
[95% CI]	[-0.221, -0.153]	[-0.232, -0.163]	[-0.252, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.038, 0.059] 0.674
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.045, 0.075] 0.620
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.065, 0.055] 0.877
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.208	-0.222	-0.235		
[95% CI]	[-0.245, -0.171]	[-0.260, -0.184]	[-0.289, -0.181]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.039, 0.067] 0.612
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.039, 0.092] 0.423
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.079, 0.053] 0.696

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.223	-0.229	-0.254		
[95% CI]	[-0.263, -0.183]	[-0.269, -0.189]	[-0.312, -0.196]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.050, 0.063] 0.826
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.039, 0.101] 0.380
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.095, 0.045] 0.486
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.227	-0.225	-0.230		
[95% CI]	[-0.268, -0.186]	[-0.267, -0.183]	[-0.290, -0.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.060, 0.057] 0.950
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.069, 0.076] 0.926
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.078, 0.067] 0.887

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.189	-0.202	-0.212		
[95% CI]	[-0.222, -0.156]	[-0.235, -0.169]	[-0.259, -0.165]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.034, 0.059] 0.594
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.035, 0.081] 0.432
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.068, 0.047] 0.724
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.207	-0.214	-0.228		
[95% CI]	[-0.242, -0.172]	[-0.250, -0.179]	[-0.278, -0.177]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.042, 0.057] 0.764
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.041, 0.082] 0.507
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.075, 0.048] 0.675

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.987	
Inter-Visit Period				0.125	
Treatment*Inter-Visit Period				0.679	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.079	-0.089	-0.103		
[95% CI]	[-0.108, -0.050]	[-0.119, -0.060]	[-0.144, -0.061]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.030, 0.052] 0.612
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.027, 0.074] 0.356
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.064, 0.038] 0.610

Produced: 17 December 2020 Page 37 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.127	-0.120	-0.129		
[95% CI]	[-0.161, -0.093]	[-0.154, -0.085]	[-0.178, -0.080]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.056, 0.041] 0.770
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.057, 0.062] 0.931
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.070, 0.050] 0.747
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.155	-0.149	-0.166		
[95% CI]	[-0.193, -0.118]	[-0.187, -0.111]	[-0.220, -0.111]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.060, 0.047] 0.810
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.056, 0.076] 0.766
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.083, 0.050] 0.623

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.167	-0.171	-0.169		
[95% CI]	[-0.208, -0.127]	[-0.212, -0.130]	[-0.227, -0.110]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.053, 0.062] 0.885
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.070, 0.073] 0.962
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.069, 0.074] 0.945
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.166	-0.170	-0.152		
[95% CI]	[-0.207, -0.125]	[-0.212, -0.128]	[-0.212, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.055, 0.063] 0.890
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.087, 0.059] 0.703
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.018 [-0.055, 0.092] 0.623

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.135	-0.131	-0.145		
[95% CI]	[-0.168, -0.102]	[-0.164, -0.097]	[-0.193, -0.097]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.051, 0.043] 0.864
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.048, 0.068] 0.739
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.073, 0.044] 0.638
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.151	-0.151	-0.153		
[95% CI]	[-0.186, -0.115]	[-0.187, -0.115]	[-0.204, -0.101]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.000 [-0.051, 0.051] 0.999
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.060, 0.065] 0.947
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.065, 0.061] 0.948

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.630	
Inter-Visit Period				0.003**	
Treatment*Inter-Visit Period				0.450	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.106	-0.118	-0.136		
[95% CI]	[-0.134, -0.077]	[-0.146, -0.089]	[-0.176, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.028, 0.052] 0.559
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.030 [-0.019, 0.080] 0.232
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.068, 0.031] 0.472

Produced: 17 December 2020 Page 41 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.171	-0.162	-0.179		
[95% CI]	[-0.206, -0.137]	[-0.197, -0.127]	[-0.229, -0.128]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.059, 0.040] 0.707
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.054, 0.068] 0.814
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.078, 0.044] 0.590
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.212	-0.181	-0.218		
[95% CI]	[-0.251, -0.174]	[-0.220, -0.142]	[-0.273, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.086, 0.024] 0.268
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.063, 0.073] 0.878
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.105, 0.032] 0.295

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.236	-0.199	-0.222		
[95% CI]	[-0.278, -0.194]	[-0.241, -0.157]	[-0.282, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.096, 0.022] 0.220
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.088, 0.059] 0.702
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.096, 0.051] 0.544
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.242	-0.201	-0.214		
[95% CI]	[-0.285, -0.199]	[-0.244, -0.157]	[-0.276, -0.152]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.103, 0.019] 0.180
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.104, 0.047] 0.461
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.089, 0.063] 0.731

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.183	-0.165	-0.193		
[95% CI]	[-0.217, -0.149]	[-0.200, -0.131]	[-0.242, -0.144]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.066, 0.030] 0.468
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.050, 0.069] 0.748
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.087, 0.032] 0.364
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.211	-0.183	-0.206		
[95% CI]	[-0.247, -0.175]	[-0.219, -0.146]	[-0.258, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.080, 0.023] 0.279
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.069, 0.058] 0.865
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.087, 0.041] 0.482

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.796	
Inter-Visit Period				0.047*	
Treatment*Inter-Visit Period				0.892	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.129	-0.118	-0.117		
[95% CI]	[-0.159, -0.100]	[-0.148, -0.088]	[-0.159, -0.075]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.053, 0.030] 0.588
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.013 [-0.064, 0.039] 0.627
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.050, 0.053] 0.963

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.199	-0.181	-0.186		
[95% CI]	[-0.235, -0.163]	[-0.217, -0.145]	[-0.238, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.069, 0.033] 0.485
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.013 [-0.076, 0.050] 0.681
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.068, 0.058] 0.878
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.230	-0.215	-0.231		
[95% CI]	[-0.269, -0.191]	[-0.255, -0.175]	[-0.288, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.071, 0.040] 0.589
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.068, 0.070] 0.974
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.086, 0.053] 0.640

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.247	-0.235	-0.242		
[95% CI]	[-0.289, -0.205]	[-0.278, -0.192]	[-0.303, -0.180]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.072, 0.048] 0.692
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.080, 0.069] 0.887
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.082, 0.068] 0.859
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.253	-0.227	-0.227		
[95% CI]	[-0.296, -0.210]	[-0.270, -0.183]	[-0.289, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.087, 0.035] 0.405
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.102, 0.050] 0.503
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.000 [-0.076, 0.076] 0.998

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12g Statistical Analysis of Average Daily Asthma Symptoms score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.205	-0.190	-0.200		
[95% CI]	[-0.240, -0.171]	[-0.225, -0.155]	[-0.250, -0.150]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.065, 0.034] 0.534
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.066, 0.055] 0.862
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.071, 0.051] 0.742
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.227	-0.210	-0.217		
[95% CI]	[-0.264, -0.191]	[-0.248, -0.173]	[-0.271, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.070, 0.035] 0.523
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.075, 0.055] 0.759
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.072, 0.058] 0.834

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	273	286	134		
Effect					
Treatment				0.470	
Inter-Visit Period				0.167	
Treatment*Inter-Visit Period				0.286	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.118	-0.127	-0.132		
[95% CI]	[-0.149, -0.087]	[-0.157, -0.096]	[-0.177, -0.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.035, 0.052] 0.691
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.040, 0.069] 0.606
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.059, 0.048] 0.843

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.166	-0.156	-0.170		
[95% CI]	[-0.203, -0.129]	[-0.193, -0.120]	[-0.223, -0.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.062, 0.042] 0.708
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.061, 0.068] 0.913
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.078, 0.051] 0.679
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.205	-0.168	-0.201		
[95% CI]	[-0.246, -0.164]	[-0.208, -0.128]	[-0.259, -0.142]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.094, 0.021] 0.212
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.075, 0.068] 0.920
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.104, 0.038] 0.363

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.231	-0.175	-0.209		
[95% CI]	[-0.276, -0.186]	[-0.219, -0.131]	[-0.273, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.056 [-0.119, 0.007] 0.079
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.022 [-0.100, 0.056] 0.576
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.034 [-0.112, 0.044] 0.390
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.227	-0.163	-0.186		
[95% CI]	[-0.275, -0.180]	[-0.209, -0.117]	[-0.253, -0.119]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.064 [-0.131, 0.002] 0.056
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.041 [-0.123, 0.041] 0.321
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.105, 0.058] 0.579

Produced: 17 December 2020

Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.179	-0.158	-0.181		
[95% CI]	[-0.216, -0.143]	[-0.193, -0.123]	[-0.232, -0.129]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.072, 0.029] 0.408
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.062, 0.064] 0.967
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.085, 0.040] 0.476
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.204	-0.164	-0.190		
[95% CI]	[-0.244, -0.165]	[-0.202, -0.125]	[-0.246, -0.133]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.096, 0.014] 0.147
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.083, 0.054] 0.670
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.094, 0.042] 0.457

Produced: 17 December 2020

Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	273	286	134		
Effect					
Treatment				0.327	
Inter-Visit Period				0.482	
Treatment*Inter-Visit Period				0.360	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.125	-0.136	-0.111		
[95% CI]	[-0.162, -0.088]	[-0.173, -0.100]	[-0.164, -0.059]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.041, 0.063] 0.671
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.078, 0.051] 0.672
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.039, 0.089] 0.441

Produced: 17 December 2020

Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.188	-0.181	-0.159		
[95% CI]	[-0.231, -0.144]	[-0.224, -0.138]	[-0.222, -0.097]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.006 [-0.068, 0.055] 0.839
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.105, 0.048] 0.465
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.022 [-0.054, 0.098] 0.567
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.243	-0.205	-0.204		
[95% CI]	[-0.291, -0.196]	[-0.251, -0.158]	[-0.271, -0.136]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.105, 0.027] 0.249
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.040 [-0.122, 0.043] 0.345
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.081, 0.082] 0.986

Produced: 17 December 2020

Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.278	-0.217	-0.207		
[95% CI]	[-0.328, -0.227]	[-0.267, -0.167]	[-0.280, -0.135]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.061 [-0.132, 0.010] 0.093
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.070 [-0.158, 0.018] 0.118
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.078, 0.097] 0.832
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.274	-0.202	-0.184		
[95% CI]	[-0.327, -0.221]	[-0.254, -0.150]	[-0.259, -0.109]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.072 [-0.146, 0.002] 0.055
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.090 [-0.182, 0.002] 0.054
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.018 [-0.073, 0.109] 0.700

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.208	-0.187	-0.176		
[95% CI]	[-0.249, -0.167]	[-0.227, -0.147]	[-0.235, -0.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.079, 0.037] 0.472
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.104, 0.040] 0.379
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.060, 0.082] 0.761
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.242	-0.198	-0.186		
[95% CI]	[-0.286, -0.198]	[-0.241, -0.156]	[-0.249, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.105, 0.018] 0.162
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.056 [-0.132, 0.020] 0.150
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.063, 0.088] 0.751

Produced: 17 December 2020

Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	273	286	134		
Effect					
Treatment				0.603	
Inter-Visit Period				0.312	
Treatment*Inter-Visit Period				0.792	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.133	-0.146	-0.156		
[95% CI]	[-0.169, -0.097]	[-0.181, -0.111]	[-0.207, -0.105]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.037, 0.063] 0.604
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.039, 0.085] 0.465
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.072, 0.052] 0.751

Produced: 17 December 2020

Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.184	-0.189	-0.211		
[95% CI]	[-0.227, -0.142]	[-0.230, -0.147]	[-0.271, -0.150]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.055, 0.064] 0.885
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.026 [-0.047, 0.100] 0.483
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.095, 0.051] 0.556
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.212	-0.208	-0.241		
[95% CI]	[-0.258, -0.166]	[-0.252, -0.163]	[-0.306, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.069, 0.060] 0.893
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.029 [-0.051, 0.108] 0.480
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.112, 0.046] 0.412

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.234	-0.202	-0.259		
[95% CI]	[-0.284, -0.183]	[-0.251, -0.152]	[-0.331, -0.187]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.103, 0.039] 0.379
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.063, 0.113] 0.574
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.057 [-0.145, 0.031] 0.201
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.230	-0.188	-0.246		
[95% CI]	[-0.283, -0.177]	[-0.240, -0.136]	[-0.322, -0.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.116, 0.033] 0.271
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.076, 0.109] 0.726
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.058 [-0.150, 0.034] 0.213

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.191	-0.192	-0.218		
[95% CI]	[-0.232, -0.151]	[-0.232, -0.153]	[-0.276, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.056, 0.058] 0.972
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.043, 0.098] 0.449
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.096, 0.044] 0.463
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.212	-0.194	-0.236		
[95% CI]	[-0.255, -0.168]	[-0.237, -0.151]	[-0.298, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.079, 0.044] 0.571
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.052, 0.101] 0.534
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.042 [-0.118, 0.034] 0.278

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	273	286	134		
Effect					
Treatment				0.589	
Inter-Visit Period				0.014*	
Treatment*Inter-Visit Period				0.259	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.087	-0.107	-0.118		
[95% CI]	[-0.123, -0.052]	[-0.141, -0.072]	[-0.169, -0.067]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.030, 0.069] 0.442
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.031, 0.092] 0.333
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.073, 0.050] 0.722

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.132	-0.110	-0.130		
[95% CI]	[-0.174, -0.090]	[-0.151, -0.069]	[-0.190, -0.070]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.022 [-0.081, 0.037] 0.457
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.076, 0.071] 0.953
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.093, 0.053] 0.587
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.162	-0.122	-0.158		
[95% CI]	[-0.209, -0.116]	[-0.167, -0.076]	[-0.225, -0.091]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.106, 0.025] 0.222
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.086, 0.077] 0.912
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.117, 0.045] 0.380

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.181	-0.130	-0.156		
[95% CI]	[-0.233, -0.129]	[-0.181, -0.080]	[-0.230, -0.082]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.050 [-0.123, 0.022] 0.173
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.025 [-0.115, 0.065] 0.588
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.115, 0.064] 0.577
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.175	-0.117	-0.121		
[95% CI]	[-0.228, -0.121]	[-0.170, -0.064]	[-0.198, -0.045]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.058 [-0.133, 0.017] 0.132
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.053 [-0.147, 0.040] 0.261
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.097, 0.089] 0.929

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.142	-0.116	-0.143		
[95% CI]	[-0.183, -0.101]	[-0.156, -0.076]	[-0.202, -0.085]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.083, 0.032] 0.377
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.070, 0.073] 0.966
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.098, 0.044] 0.448
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.160	-0.120	-0.142		
[95% CI]	[-0.205, -0.115]	[-0.164, -0.076]	[-0.206, -0.077]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.103, 0.023] 0.215
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.097, 0.060] 0.647
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.099, 0.056] 0.587

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	273	286	134		
Effect					
Treatment				0.195	
Inter-Visit Period				0.007**	
Treatment*Inter-Visit Period				0.211	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.125	-0.117	-0.144		
[95% CI]	[-0.161, -0.089]	[-0.152, -0.082]	[-0.195, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.058, 0.042] 0.747
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.044, 0.081] 0.562
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.089, 0.035] 0.398

Produced: 17 December 2020 Page 17 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.160	-0.145	-0.180		
[95% CI]	[-0.203, -0.117]	[-0.187, -0.103]	[-0.241, -0.119]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.075, 0.045] 0.629
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.055, 0.095] 0.598
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.109, 0.039] 0.357
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.200	-0.138	-0.203		
[95% CI]	[-0.248, -0.151]	[-0.186, -0.091]	[-0.272, -0.133]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.061 [-0.129, 0.006] 0.076
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.082, 0.087] 0.952
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.148, 0.020] 0.134

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.232	-0.150	-0.216		
[95% CI]	[-0.284, -0.179]	[-0.201, -0.099]	[-0.291, -0.142]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.082 [-0.155, -0.008] 0.029*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.107, 0.075] 0.737
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.066 [-0.156, 0.024] 0.153
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.232	-0.145	-0.196		
[95% CI]	[-0.287, -0.177]	[-0.199, -0.091]	[-0.274, -0.118]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.087 [-0.164, -0.010] 0.027*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.036 [-0.132, 0.060] 0.460
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.051 [-0.146, 0.044] 0.295

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.176	-0.137	-0.186		
[95% CI]	[-0.218, -0.134]	[-0.179, -0.096]	[-0.247, -0.126]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.098, 0.020] 0.197
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.063, 0.084] 0.781
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.049 [-0.123, 0.024] 0.186
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.204	-0.143	-0.197		
[95% CI]	[-0.250, -0.158]	[-0.187, -0.098]	[-0.262, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.061 [-0.125, 0.002] 0.060
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.087, 0.072] 0.857
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.133, 0.025] 0.179

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	273	285	134		
Effect					
Treatment				0.464	
Inter-Visit Period				0.024*	
Treatment*Inter-Visit Period				0.983	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.147	-0.119	-0.139		
[95% CI]	[-0.185, -0.108]	[-0.157, -0.082]	[-0.194, -0.085]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.081, 0.026] 0.321
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.074, 0.059] 0.832
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.086, 0.046] 0.556

Produced: 17 December 2020 Page 21 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.206	-0.169	-0.187		
[95% CI]	[-0.251, -0.161]	[-0.213, -0.124]	[-0.252, -0.123]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.100, 0.026] 0.248
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.097, 0.060] 0.645
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.097, 0.059] 0.637
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.234	-0.195	-0.230		
[95% CI]	[-0.282, -0.185]	[-0.243, -0.147]	[-0.299, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.107, 0.030] 0.271
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.089, 0.081] 0.932
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.119, 0.050] 0.421

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.256	-0.212	-0.233		
[95% CI]	[-0.309, -0.203]	[-0.264, -0.160]	[-0.308, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.118, 0.030] 0.247
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.115, 0.070] 0.627
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.113, 0.071] 0.653
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.241	-0.196	-0.216		
[95% CI]	[-0.296, -0.186]	[-0.250, -0.142]	[-0.294, -0.138]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.122, 0.032] 0.253
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.025 [-0.120, 0.070] 0.606
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.115, 0.075] 0.683

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.212	-0.175	-0.203		
[95% CI]	[-0.255, -0.168]	[-0.218, -0.133]	[-0.265, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.097, 0.025] 0.242
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.084, 0.067] 0.820
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.103, 0.048] 0.473
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.230	-0.190	-0.214		
[95% CI]	[-0.277, -0.184]	[-0.235, -0.144]	[-0.280, -0.148]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.105, 0.025] 0.224
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.097, 0.065] 0.692
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.104, 0.056] 0.558

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.925	
Inter-Visit Period				0.048*	
Treatment*Inter-Visit Period				0.688	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.120	-0.113	-0.143		
[95% CI]	[-0.151, -0.090]	[-0.144, -0.081]	[-0.186, -0.100]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.051, 0.037] 0.748
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.030, 0.076] 0.391
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.083, 0.023] 0.264

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.182	-0.181	-0.196		
[95% CI]	[-0.220, -0.144]	[-0.220, -0.142]	[-0.249, -0.143]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.055, 0.053] 0.972
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.051, 0.079] 0.674
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.081, 0.051] 0.655
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.215	-0.222	-0.231		
[95% CI]	[-0.258, -0.173]	[-0.265, -0.178]	[-0.291, -0.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.055, 0.068] 0.835
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.058, 0.089] 0.674
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.083, 0.065] 0.805

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.223	-0.239	-0.244		
[95% CI]	[-0.269, -0.177]	[-0.286, -0.192]	[-0.309, -0.180]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.016 [-0.050, 0.081] 0.636
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.058, 0.100] 0.597
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.085, 0.074] 0.893
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.242	-0.248	-0.233		
[95% CI]	[-0.290, -0.195]	[-0.297, -0.199]	[-0.300, -0.166]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.063, 0.074] 0.872
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.092, 0.073] 0.823
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.068, 0.098] 0.723

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.190	-0.192	-0.207		
[95% CI]	[-0.228, -0.153]	[-0.231, -0.154]	[-0.259, -0.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.051, 0.056] 0.939
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.048, 0.080] 0.618
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.079, 0.050] 0.666
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.211	-0.218	-0.223		
[95% CI]	[-0.251, -0.171]	[-0.259, -0.177]	[-0.279, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.051, 0.064] 0.822
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.057, 0.081] 0.739
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.075, 0.065] 0.885

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.985	
Inter-Visit Period				0.033*	
Treatment*Inter-Visit Period				0.392	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.139	-0.141	-0.146		
[95% CI]	[-0.174, -0.104]	[-0.177, -0.105]	[-0.194, -0.098]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.048, 0.052] 0.934
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.052, 0.067] 0.813
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.065, 0.055] 0.868

Produced: 17 December 2020 Page 29 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.206	-0.219	-0.214		
[95% CI]	[-0.249, -0.163]	[-0.264, -0.175]	[-0.274, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.049, 0.075] 0.670
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.067, 0.082] 0.836
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.006 [-0.070, 0.081] 0.884
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.253	-0.261	-0.265		
[95% CI]	[-0.301, -0.205]	[-0.310, -0.212]	[-0.332, -0.197]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.061, 0.077] 0.824
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.071, 0.094] 0.782
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.087, 0.080] 0.927

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.261	-0.275	-0.289		
[95% CI]	[-0.312, -0.211]	[-0.327, -0.223]	[-0.361, -0.218]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.059, 0.086] 0.721
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.028 [-0.059, 0.116] 0.529
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.103, 0.073] 0.742
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.292	-0.277	-0.263		
[95% CI]	[-0.345, -0.239]	[-0.331, -0.223]	[-0.338, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.091, 0.061] 0.697
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.029 [-0.120, 0.062] 0.534
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.014 [-0.078, 0.106] 0.766

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.221	-0.230	-0.231		
[95% CI]	[-0.262, -0.180]	[-0.272, -0.187]	[-0.289, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.051, 0.068] 0.774
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.061, 0.081] 0.787
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.073, 0.071] 0.975
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.248	-0.253	-0.254		
[95% CI]	[-0.292, -0.204]	[-0.298, -0.208]	[-0.316, -0.192]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.058, 0.067] 0.890
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.070, 0.081] 0.881
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.078, 0.075] 0.972

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.896	
Inter-Visit Period				0.076	
Treatment*Inter-Visit Period				0.539	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.138	-0.126	-0.172		
[95% CI]	[-0.172, -0.103]	[-0.162, -0.090]	[-0.221, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.061, 0.038] 0.652
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.025, 0.094] 0.256
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.046 [-0.106, 0.014] 0.134

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.196	-0.200	-0.215		
[95% CI]	[-0.238, -0.153]	[-0.243, -0.156]	[-0.274, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.057, 0.065] 0.895
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.054, 0.092] 0.610
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.088, 0.059] 0.691
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.223	-0.234	-0.240		
[95% CI]	[-0.270, -0.175]	[-0.282, -0.185]	[-0.306, -0.174]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.056, 0.079] 0.746
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.064, 0.099] 0.670
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.088, 0.075] 0.877

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.232	-0.250	-0.256		
[95% CI]	[-0.283, -0.182]	[-0.302, -0.198]	[-0.327, -0.185]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.018 [-0.055, 0.090] 0.634
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.063, 0.111] 0.592
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.094, 0.081] 0.890
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.248	-0.261	-0.237		
[95% CI]	[-0.300, -0.197]	[-0.314, -0.208]	[-0.310, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.062, 0.086] 0.746
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.101, 0.078] 0.805
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.067, 0.114] 0.610

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.201	-0.207	-0.222		
[95% CI]	[-0.242, -0.160]	[-0.249, -0.164]	[-0.280, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.054, 0.065] 0.855
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.050, 0.092] 0.568
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.087, 0.056] 0.678
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.221	-0.231	-0.235		
[95% CI]	[-0.264, -0.177]	[-0.276, -0.186]	[-0.296, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.053, 0.073] 0.748
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.062, 0.090] 0.715
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.080, 0.073] 0.922

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.793	
Inter-Visit Period				0.188	
Treatment*Inter-Visit Period				0.415	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.087	-0.075	-0.114		
[95% CI]	[-0.123, -0.052]	[-0.112, -0.039]	[-0.164, -0.065]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.063, 0.039] 0.650
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.034, 0.088] 0.386
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.100, 0.023] 0.217

Produced: 17 December 2020 Page 37 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.137	-0.133	-0.162		
[95% CI]	[-0.179, -0.096]	[-0.175, -0.090]	[-0.220, -0.104]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.064, 0.055] 0.881
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.047, 0.096] 0.503
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.029 [-0.101, 0.043] 0.430
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.161	-0.180	-0.179		
[95% CI]	[-0.207, -0.115]	[-0.227, -0.133]	[-0.244, -0.114]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.047, 0.085] 0.579
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.062, 0.097] 0.659
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.079, 0.081] 0.985

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.163	-0.202	-0.195		
[95% CI]	[-0.212, -0.113]	[-0.253, -0.151]	[-0.265, -0.125]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.039 [-0.032, 0.110] 0.279
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.032 [-0.053, 0.118] 0.458
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.007 [-0.079, 0.093] 0.875
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.179	-0.216	-0.186		
[95% CI]	[-0.231, -0.128]	[-0.269, -0.163]	[-0.259, -0.114]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.037 [-0.037, 0.110] 0.326
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.082, 0.096] 0.877
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.030 [-0.060, 0.119] 0.514

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.143	-0.149	-0.164		
[95% CI]	[-0.183, -0.102]	[-0.191, -0.108]	[-0.221, -0.107]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.051, 0.065] 0.818
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.049, 0.091] 0.551
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.085, 0.056] 0.688
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.156	-0.179	-0.177		
[95% CI]	[-0.200, -0.113]	[-0.224, -0.134]	[-0.239, -0.116]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.022 [-0.040, 0.085] 0.480
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.054, 0.096] 0.584
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.074, 0.077] 0.969

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.855	
Inter-Visit Period				0.003**	
Treatment*Inter-Visit Period				0.965	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.117	-0.108	-0.139		
[95% CI]	[-0.152, -0.081]	[-0.145, -0.072]	[-0.189, -0.090]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.059, 0.042] 0.744
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.039, 0.083] 0.475
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.092, 0.031] 0.328

Produced: 17 December 2020 Page 41 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.190	-0.171	-0.191		
[95% CI]	[-0.233, -0.146]	[-0.215, -0.126]	[-0.252, -0.130]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.082, 0.043] 0.547
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.074, 0.076] 0.972
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.096, 0.055] 0.595
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.228	-0.212	-0.237		
[95% CI]	[-0.276, -0.180]	[-0.261, -0.162]	[-0.304, -0.170]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.085, 0.053] 0.647
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.073, 0.092] 0.817
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.109, 0.057] 0.544

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.240	-0.229	-0.235		
[95% CI]	[-0.292, -0.188]	[-0.282, -0.176]	[-0.308, -0.162]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.086, 0.063] 0.764
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.095, 0.084] 0.909
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.097, 0.084] 0.893
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.253	-0.238	-0.244		
[95% CI]	[-0.307, -0.200]	[-0.292, -0.183]	[-0.320, -0.169]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.093, 0.061] 0.685
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.102, 0.084] 0.848
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.100, 0.087] 0.886

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.199	-0.183	-0.208		
[95% CI]	[-0.241, -0.157]	[-0.226, -0.140]	[-0.267, -0.149]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.076, 0.045] 0.608
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.064, 0.082] 0.807
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.098, 0.048] 0.505
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.223	-0.208	-0.224		
[95% CI]	[-0.268, -0.177]	[-0.254, -0.161]	[-0.287, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-0.080, 0.050] 0.658
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.077, 0.079] 0.979
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.095, 0.063] 0.696

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.857	
Inter-Visit Period				0.100	
Treatment*Inter-Visit Period				0.672	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.131	-0.110	-0.131		
[95% CI]	[-0.167, -0.095]	[-0.148, -0.073]	[-0.182, -0.081]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.072, 0.032] 0.440
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.062, 0.063] 0.986
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.084, 0.042] 0.511

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.203	-0.180	-0.207		
[95% CI]	[-0.247, -0.159]	[-0.225, -0.134]	[-0.269, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.087, 0.039] 0.461
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.072, 0.080] 0.922
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.104, 0.049] 0.481
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.237	-0.228	-0.246		
[95% CI]	[-0.286, -0.189]	[-0.277, -0.178]	[-0.314, -0.178]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.079, 0.060] 0.790
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.075, 0.092] 0.837
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.102, 0.066] 0.672

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.245	-0.248	-0.259		
[95% CI]	[-0.297, -0.193]	[-0.302, -0.195]	[-0.332, -0.185]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.071, 0.078] 0.926
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.076, 0.104] 0.763
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.101, 0.080] 0.823
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.271	-0.247	-0.255		
[95% CI]	[-0.325, -0.218]	[-0.302, -0.192]	[-0.331, -0.179]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.101, 0.052] 0.532
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.017 [-0.110, 0.076] 0.723
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.102, 0.086] 0.872

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12h Statistical Analysis of Average Daily Asthma Symptoms score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.210	-0.195	-0.216		
[95% CI]	[-0.253, -0.168]	[-0.239, -0.151]	[-0.276, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.077, 0.046] 0.618
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.067, 0.079] 0.874
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.095, 0.053] 0.569
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.234	-0.221	-0.237		
[95% CI]	[-0.279, -0.188]	[-0.268, -0.175]	[-0.300, -0.173]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.078, 0.053] 0.707
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.075, 0.081] 0.944
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.094, 0.064] 0.704

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.440	
Inter-Visit Period				0.191	
Treatment*Inter-Visit Period				0.524	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.103	-0.107	-0.135		
[95% CI]	[-0.133, -0.074]	[-0.137, -0.078]	[-0.177, -0.094]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.038, 0.046] 0.854
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.032 [-0.019, 0.083] 0.222
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.079, 0.023] 0.284

Produced: 17 December 2020 Page 1 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.161	-0.148	-0.183		
[95% CI]	[-0.197, -0.125]	[-0.184, -0.112]	[-0.234, -0.132]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.064, 0.038] 0.609
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.040, 0.084] 0.494
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.097, 0.027] 0.271
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.198	-0.174	-0.223		
[95% CI]	[-0.238, -0.158]	[-0.214, -0.134]	[-0.279, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.080, 0.032] 0.402
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.044, 0.094] 0.475
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.049 [-0.118, 0.020] 0.162

Produced: 17 December 2020

Page 2 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.215	-0.186	-0.229		
[95% CI]	[-0.258, -0.172]	[-0.230, -0.143]	[-0.290, -0.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.090, 0.032] 0.354
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.061, 0.089] 0.720
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.043 [-0.118, 0.032] 0.265
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.226	-0.177	-0.213		
[95% CI]	[-0.272, -0.181]	[-0.223, -0.131]	[-0.277, -0.148]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.049 [-0.114, 0.015] 0.132
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.093, 0.065] 0.733
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.115, 0.043] 0.375

Produced: 17 December 2020

Page 3 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.172	-0.156	-0.197		
[95% CI]	[-0.207, -0.137]	[-0.191, -0.120]	[-0.247, -0.147]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.066, 0.033] 0.518
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.036, 0.086] 0.420
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.041 [-0.103, 0.020] 0.182
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.196	-0.169	-0.209		
[95% CI]	[-0.234, -0.158]	[-0.207, -0.131]	[-0.263, -0.156]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.081, 0.026] 0.318
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.053, 0.079] 0.697
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.106, 0.025] 0.228

Produced: 17 December 2020 Page 4 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.267	
Inter-Visit Period				0.156	
Treatment*Inter-Visit Period				0.114	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.120	-0.124	-0.148		
[95% CI]	[-0.155, -0.086]	[-0.159, -0.090]	[-0.196, -0.099]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.045, 0.053] 0.876
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.032, 0.087] 0.370
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.083, 0.036] 0.442

Produced: 17 December 2020 Page 5 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.203	-0.169	-0.214		
[95% CI]	[-0.245, -0.161]	[-0.211, -0.127]	[-0.273, -0.155]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.094, 0.025] 0.253
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.062, 0.083] 0.775
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.045 [-0.118, 0.028] 0.223
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.261	-0.206	-0.248		
[95% CI]	[-0.306, -0.215]	[-0.251, -0.160]	[-0.313, -0.184]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.119, 0.010] 0.095
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-0.091, 0.066] 0.756
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.042 [-0.121, 0.036] 0.291

Produced: 17 December 2020

Page 6 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.284	-0.226	-0.256		
[95% CI]	[-0.332, -0.235]	[-0.275, -0.178]	[-0.325, -0.187]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.126, 0.012] 0.104
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.112, 0.056] 0.516
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.029 [-0.114, 0.055] 0.497
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.303	-0.217	-0.233		
[95% CI]	[-0.354, -0.252]	[-0.269, -0.166]	[-0.306, -0.160]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.158, -0.013] 0.021*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.070 [-0.159, 0.019] 0.124
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.105, 0.073] 0.727

Produced: 17 December 2020

Page 7 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.222	-0.182	-0.222		
[95% CI]	[-0.261, -0.182]	[-0.222, -0.142]	[-0.279, -0.166]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.096, 0.017] 0.168
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.068, 0.070] 0.984
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.109, 0.029] 0.251
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.257	-0.202	-0.234		
[95% CI]	[-0.299, -0.215]	[-0.244, -0.160]	[-0.294, -0.174]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.115, 0.005] 0.072
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.097, 0.050] 0.533
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.105, 0.042] 0.396

Produced: 17 December 2020 Page 8 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.207	
Inter-Visit Period				0.450	
Treatment*Inter-Visit Period				0.500	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.125	-0.119	-0.150		
[95% CI]	[-0.158, -0.091]	[-0.152, -0.085]	[-0.197, -0.103]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.006 [-0.053, 0.041] 0.797
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.032, 0.083] 0.386
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.089, 0.026] 0.282

Produced: 17 December 2020 Page 9 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.173	-0.171	-0.211		
[95% CI]	[-0.213, -0.133]	[-0.210, -0.131]	[-0.267, -0.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.058, 0.054] 0.937
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [-0.031, 0.106] 0.283
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.040 [-0.109, 0.029] 0.255
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.194	-0.187	-0.261		
[95% CI]	[-0.238, -0.150]	[-0.231, -0.143]	[-0.323, -0.199]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.069, 0.055] 0.830
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.067 [-0.009, 0.143] 0.085
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.074 [-0.150, 0.002] 0.058

Produced: 17 December 2020 Page 10 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.212	-0.191	-0.273		
[95% CI]	[-0.259, -0.164]	[-0.238, -0.143]	[-0.341, -0.206]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.088, 0.046] 0.540
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.061 [-0.021, 0.144] 0.144
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.082 [-0.165, 0.000] 0.050
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.225	-0.183	-0.257		
[95% CI]	[-0.275, -0.175]	[-0.233, -0.133]	[-0.328, -0.186]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.112, 0.029] 0.248
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.033 [-0.054, 0.119] 0.461
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.074 [-0.161, 0.013] 0.093

Produced: 17 December 2020 Page 11 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.177	-0.172	-0.228		
[95% CI]	[-0.216, -0.138]	[-0.210, -0.133]	[-0.283, -0.174]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.060, 0.049] 0.849
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.052 [-0.015, 0.118] 0.130
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.057 [-0.124, 0.010] 0.095
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.197	-0.179	-0.247		
[95% CI]	[-0.239, -0.156]	[-0.221, -0.138]	[-0.306, -0.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.077, 0.041] 0.549
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.050 [-0.022, 0.122] 0.175
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.068 [-0.140, 0.004] 0.065

Produced: 17 December 2020 Page 12 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.879	
Inter-Visit Period				0.044*	
Treatment*Inter-Visit Period				0.693	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.066	-0.079	-0.105		
[95% CI]	[-0.100, -0.032]	[-0.113, -0.045]	[-0.152, -0.057]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.036, 0.061] 0.610
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [-0.021, 0.097] 0.203
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.084, 0.033] 0.392

Produced: 17 December 2020 Page 13 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.117	-0.110	-0.131		
[95% CI]	[-0.156, -0.077]	[-0.150, -0.070]	[-0.187, -0.074]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.063, 0.049] 0.810
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.055, 0.083] 0.693
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.090, 0.048] 0.554
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.149	-0.141	-0.163		
[95% CI]	[-0.193, -0.105]	[-0.185, -0.097]	[-0.225, -0.100]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.070, 0.055] 0.816
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.062, 0.090] 0.721
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.098, 0.055] 0.584

Produced: 17 December 2020 Page 14 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.154	-0.152	-0.169		
[95% CI]	[-0.202, -0.105]	[-0.200, -0.104]	[-0.237, -0.100]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.070, 0.067] 0.968
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.069, 0.099] 0.723
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.100, 0.067] 0.698
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.161	-0.144	-0.147		
[95% CI]	[-0.211, -0.112]	[-0.194, -0.094]	[-0.218, -0.076]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.089, 0.053] 0.619
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.101, 0.072] 0.739
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.090, 0.083] 0.943

Produced: 17 December 2020 Page 15 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.126	-0.122	-0.144		
[95% CI]	[-0.165, -0.087]	[-0.161, -0.083]	[-0.199, -0.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.059, 0.051] 0.881
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.050, 0.085] 0.608
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.089, 0.046] 0.526
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.142	-0.135	-0.151		
[95% CI]	[-0.184, -0.100]	[-0.177, -0.093]	[-0.211, -0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.066, 0.053] 0.828
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.063, 0.082] 0.799
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.089, 0.057] 0.665

Produced: 17 December 2020 Page 16 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.475	
Inter-Visit Period				0.009**	
Treatment*Inter-Visit Period				0.519	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.102	-0.107	-0.137		
[95% CI]	[-0.136, -0.068]	[-0.142, -0.073]	[-0.185, -0.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.043, 0.054] 0.832
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.024, 0.094] 0.246
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.089, 0.030] 0.324

Produced: 17 December 2020 Page 17 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.153	-0.143	-0.174		
[95% CI]	[-0.195, -0.111]	[-0.184, -0.101]	[-0.232, -0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.069, 0.049] 0.730
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.051, 0.093] 0.575
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.103, 0.041] 0.400
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.191	-0.161	-0.217		
[95% CI]	[-0.237, -0.145]	[-0.208, -0.115]	[-0.282, -0.152]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.095, 0.036] 0.376
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.026 [-0.054, 0.106] 0.521
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.135, 0.024] 0.173

Produced: 17 December 2020 Page 18 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.215	-0.176	-0.215		
[95% CI]	[-0.265, -0.165]	[-0.226, -0.126]	[-0.286, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.110, 0.032] 0.279
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.000 [-0.087, 0.086] 0.999
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.126, 0.048] 0.377
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.221	-0.164	-0.211		
[95% CI]	[-0.272, -0.169]	[-0.216, -0.112]	[-0.284, -0.137]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.130, 0.016] 0.128
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.100, 0.080] 0.830
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.137, 0.043] 0.305

Produced: 17 December 2020 Page 19 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.165	-0.147	-0.191		
[95% CI]	[-0.206, -0.125]	[-0.188, -0.106]	[-0.249, -0.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.076, 0.039] 0.535
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.026 [-0.045, 0.096] 0.473
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-0.115, 0.027] 0.221
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.192	-0.159	-0.202		
[95% CI]	[-0.235, -0.148]	[-0.203, -0.115]	[-0.264, -0.141]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-0.094, 0.029] 0.297
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.065, 0.086] 0.783
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.043 [-0.119, 0.032] 0.260

Produced: 17 December 2020 Page 20 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.305	
Inter-Visit Period				0.067	
Treatment*Inter-Visit Period				0.664	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.119	-0.102	-0.137		
[95% CI]	[-0.154, -0.085]	[-0.137, -0.068]	[-0.186, -0.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.066, 0.031] 0.487
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.041, 0.078] 0.552
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.095, 0.024] 0.245

Produced: 17 December 2020 Page 21 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.193	-0.149	-0.206		
[95% CI]	[-0.236, -0.151]	[-0.191, -0.106]	[-0.265, -0.146]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.105, 0.015] 0.142
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.061, 0.085] 0.744
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.057 [-0.130, 0.016] 0.127
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.228	-0.183	-0.245		
[95% CI]	[-0.274, -0.182]	[-0.230, -0.137]	[-0.310, -0.180]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.110, 0.021] 0.183
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.063, 0.097] 0.674
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.142, 0.019] 0.132

Produced: 17 December 2020 Page 22 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.235	-0.206	-0.247		
[95% CI]	[-0.286, -0.185]	[-0.257, -0.155]	[-0.319, -0.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.101, 0.043] 0.425
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.076, 0.100] 0.794
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.041 [-0.129, 0.047] 0.363
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.246	-0.195	-0.241		
[95% CI]	[-0.298, -0.193]	[-0.248, -0.143]	[-0.315, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.050 [-0.124, 0.024] 0.183
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.095, 0.086] 0.926
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.046 [-0.137, 0.045] 0.321

Produced: 17 December 2020 Page 23 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.200	-0.160	-0.216		
[95% CI]	[-0.241, -0.160]	[-0.201, -0.119]	[-0.274, -0.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.098, 0.018] 0.172
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.055, 0.087] 0.662
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.127, 0.015] 0.121
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.220	-0.181	-0.230		
[95% CI]	[-0.264, -0.176]	[-0.225, -0.137]	[-0.292, -0.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.102, 0.023] 0.212
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.066, 0.086] 0.796
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.050 [-0.126, 0.027] 0.201

Produced: 17 December 2020 Page 24 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
Average Total Daily Asthma Symptoms Score					
Number of Patients Included in Model	252	251	127		
Effect					
Treatment				0.935	
Inter-Visit Period				0.077	
Treatment*Inter-Visit Period				0.904	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.139	-0.135	-0.142		
[95% CI]	[-0.171, -0.107]	[-0.168, -0.103]	[-0.187, -0.096]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.049, 0.042] 0.877
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.053, 0.059] 0.921
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.062, 0.049] 0.821

Produced: 17 December 2020 Page 25 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.191	-0.194	-0.186		
[95% CI]	[-0.230, -0.152]	[-0.233, -0.154]	[-0.241, -0.131]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.053, 0.058] 0.929
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.073, 0.063] 0.886
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.007 [-0.060, 0.075] 0.829
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.225	-0.220	-0.211		
[95% CI]	[-0.269, -0.181]	[-0.265, -0.176]	[-0.273, -0.148]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.068, 0.058] 0.881
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.091, 0.062] 0.714
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.010 [-0.067, 0.086] 0.808

Produced: 17 December 2020 Page 26 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.241	-0.232	-0.229		
[95% CI]	[-0.289, -0.193]	[-0.280, -0.184]	[-0.297, -0.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.077, 0.059] 0.794
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-0.095, 0.071] 0.770
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.080, 0.086] 0.938
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.244	-0.242	-0.211		
[95% CI]	[-0.294, -0.194]	[-0.292, -0.192]	[-0.281, -0.140]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.073, 0.068] 0.950
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.034 [-0.120, 0.053] 0.445
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.031 [-0.055, 0.118] 0.477

Produced: 17 December 2020 Page 27 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Total Daily Asthma Symptoms Score					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.201	-0.199	-0.193		
[95% CI]	[-0.240, -0.163]	[-0.238, -0.160]	[-0.247, -0.138]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.057, 0.052] 0.932
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.075, 0.058] 0.795
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.006 [-0.060, 0.073] 0.850
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.222	-0.218	-0.206		
[95% CI]	[-0.264, -0.180]	[-0.260, -0.176]	[-0.266, -0.147]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.063, 0.055] 0.891
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.088, 0.057] 0.675
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.011 [-0.061, 0.084] 0.759

Produced: 17 December 2020 Page 28 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Number of Patients Included in Model	252	251	127		
Effect					
Treatment				0.384	
Inter-Visit Period				0.227	
Treatment*Inter-Visit Period				0.448	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.148	-0.157	-0.108		
[95% CI]	[-0.184, -0.111]	[-0.194, -0.120]	[-0.160, -0.056]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.043, 0.061] 0.734
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.040 [-0.103, 0.024] 0.222
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.049 [-0.015, 0.112] 0.134

Produced: 17 December 2020 Page 29 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.189	-0.239	-0.157		
[95% CI]	[-0.234, -0.144]	[-0.284, -0.194]	[-0.220, -0.093]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.050 [-0.014, 0.114] 0.122
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.033 [-0.111, 0.045] 0.412
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.083 [0.005, 0.161] 0.037*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.232	-0.266	-0.222		
[95% CI]	[-0.282, -0.182]	[-0.316, -0.215]	[-0.292, -0.151]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.033 [-0.038, 0.104] 0.357
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.097, 0.076] 0.809
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.044 [-0.043, 0.131] 0.320

Produced: 17 December 2020 Page 30 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.250	-0.269	-0.245		
[95% CI]	[-0.303, -0.197]	[-0.323, -0.216]	[-0.321, -0.170]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.056, 0.094] 0.620
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.097, 0.087] 0.916
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.068, 0.116] 0.609
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.257	-0.267	-0.217		
[95% CI]	[-0.311, -0.202]	[-0.322, -0.213]	[-0.294, -0.140]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.067, 0.088] 0.789
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.040 [-0.134, 0.055] 0.409
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.050 [-0.044, 0.145] 0.297

Produced: 17 December 2020 Page 31 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Cough					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.206	-0.241	-0.184		
[95% CI]	[-0.249, -0.163]	[-0.284, -0.198]	[-0.244, -0.124]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.035 [-0.026, 0.095] 0.259
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.022 [-0.096, 0.052] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.057 [-0.017, 0.131] 0.133
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.230	-0.255	-0.208		
[95% CI]	[-0.275, -0.184]	[-0.300, -0.209]	[-0.272, -0.144]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.025 [-0.039, 0.089] 0.447
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.100, 0.057] 0.592
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.046 [-0.032, 0.125] 0.248

Produced: 17 December 2020 Page 32 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Number of Patients Included in Model	252	251	127		
Effect					
Treatment				0.830	
Inter-Visit Period				0.064	
Treatment*Inter-Visit Period				0.587	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.149	-0.158	-0.183		
[95% CI]	[-0.186, -0.111]	[-0.196, -0.120]	[-0.236, -0.131]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.044, 0.063] 0.726
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.030, 0.100] 0.290
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.090, 0.039] 0.441

Produced: 17 December 2020 Page 33 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.212	-0.223	-0.217		
[95% CI]	[-0.257, -0.166]	[-0.269, -0.178]	[-0.282, -0.153]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.053, 0.076] 0.730
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.073, 0.084] 0.889
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.006 [-0.073, 0.084] 0.887
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.246	-0.262	-0.216		
[95% CI]	[-0.296, -0.197]	[-0.311, -0.212]	[-0.286, -0.147]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.015 [-0.055, 0.085] 0.664
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.030 [-0.116, 0.055] 0.490
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.046 [-0.040, 0.131] 0.296

Produced: 17 December 2020 Page 34 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Wheeze					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.259	-0.270	-0.241		
[95% CI]	[-0.313, -0.205]	[-0.324, -0.216]	[-0.317, -0.164]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.065, 0.087] 0.778
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.019 [-0.112, 0.075] 0.694
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.030 [-0.064, 0.123] 0.533
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.256	-0.277	-0.224		
[95% CI]	[-0.312, -0.201]	[-0.333, -0.221]	[-0.302, -0.145]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.021 [-0.058, 0.099] 0.606
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.128, 0.064] 0.507
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.053 [-0.043, 0.149] 0.279

Produced: 17 December 2020 Page 35 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Athma Symptom Score: Wheeze					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.221	-0.234	-0.212		
[95% CI]	[-0.264, -0.177]	[-0.277, -0.191]	[-0.273, -0.150]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.048, 0.075] 0.671
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.084, 0.066] 0.812
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.022 [-0.053, 0.097] 0.558
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.239	-0.254	-0.222		
[95% CI]	[-0.286, -0.193]	[-0.300, -0.207]	[-0.288, -0.156]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.052, 0.080] 0.670
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.017 [-0.098, 0.064] 0.678
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.031 [-0.049, 0.112] 0.445

Produced: 17 December 2020 Page 36 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Number of Patients Included in Model	252	251	127		
Effect					
Treatment				0.935	
Inter-Visit Period				0.010**	
Treatment*Inter-Visit Period				0.768	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.114	-0.107	-0.130		
[95% CI]	[-0.151, -0.077]	[-0.144, -0.069]	[-0.182, -0.077]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.060, 0.046] 0.794
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.048, 0.080] 0.624
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.087, 0.041] 0.482

Produced: 17 December 2020 Page 37 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.158	-0.136	-0.169		
[95% CI]	[-0.202, -0.114]	[-0.180, -0.092]	[-0.231, -0.107]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.022 [-0.085, 0.040] 0.482
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.065, 0.087] 0.781
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.109, 0.043] 0.393
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.178	-0.162	-0.179		
[95% CI]	[-0.227, -0.128]	[-0.212, -0.112]	[-0.248, -0.109]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.086, 0.054] 0.658
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.085, 0.086] 0.988
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.102, 0.069] 0.706

Produced: 17 December 2020 Page 38 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.194	-0.183	-0.188		
[95% CI]	[-0.247, -0.140]	[-0.237, -0.130]	[-0.263, -0.112]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.086, 0.065] 0.790
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.099, 0.087] 0.900
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.097, 0.088] 0.926
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.196	-0.196	-0.167		
[95% CI]	[-0.251, -0.140]	[-0.252, -0.140]	[-0.246, -0.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.078, 0.080] 0.983
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.028 [-0.125, 0.068] 0.567
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.029 [-0.068, 0.126] 0.555

Produced: 17 December 2020 Page 39 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Chest Tightness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.162	-0.145	-0.168		
[95% CI]	[-0.205, -0.119]	[-0.189, -0.102]	[-0.229, -0.107]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.077, 0.045] 0.596
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.068, 0.081] 0.872
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.097, 0.052] 0.552
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.178	-0.167	-0.173		
[95% CI]	[-0.225, -0.131]	[-0.214, -0.120]	[-0.239, -0.107]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.077, 0.056] 0.749
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.086, 0.076] 0.903
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.087, 0.075] 0.889

Produced: 17 December 2020 Page 40 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Number of Patients Included in Model	252	251	127		
Effect					
Treatment				0.429	
Inter-Visit Period				0.020*	
Treatment*Inter-Visit Period				0.864	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.145	-0.119	-0.147		
[95% CI]	[-0.182, -0.107]	[-0.157, -0.082]	[-0.200, -0.095]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.078, 0.027] 0.346
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.062, 0.067] 0.935
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.093, 0.036] 0.393

Produced: 17 December 2020 Page 41 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.204	-0.175	-0.203		
[95% CI]	[-0.249, -0.159]	[-0.221, -0.130]	[-0.267, -0.139]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.029 [-0.093, 0.035] 0.380
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.079, 0.077] 0.976
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.106, 0.051] 0.491
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.243	-0.191	-0.229		
[95% CI]	[-0.294, -0.193]	[-0.242, -0.140]	[-0.301, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.052 [-0.124, 0.020] 0.155
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.103, 0.073] 0.745
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.126, 0.050] 0.401

Produced: 17 December 2020 Page 42 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.262	-0.205	-0.245		
[95% CI]	[-0.317, -0.207]	[-0.261, -0.150]	[-0.323, -0.167]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.056 [-0.134, 0.022] 0.158
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.017 [-0.112, 0.079] 0.733
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.135, 0.056] 0.416
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.269	-0.227	-0.239		
[95% CI]	[-0.327, -0.211]	[-0.285, -0.169]	[-0.320, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.124, 0.039] 0.309
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.030 [-0.130, 0.070] 0.552
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.112, 0.088] 0.812

Produced: 17 December 2020 Page 43 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Daily Asthma Symptom Score: Breathlessness					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.216	-0.175	-0.208		
[95% CI]	[-0.260, -0.172]	[-0.219, -0.131]	[-0.271, -0.146]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.103, 0.022] 0.200
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.084, 0.069] 0.841
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.109, 0.043] 0.395
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.241	-0.195	-0.225		
[95% CI]	[-0.289, -0.192]	[-0.243, -0.147]	[-0.293, -0.157]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.113, 0.023] 0.192
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.099, 0.068] 0.717
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.030 [-0.113, 0.053] 0.480

Produced: 17 December 2020 Page 44 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Number of Patients Included in Model	252	250	127		
Effect					
Treatment				0.792	
Inter-Visit Period				0.127	
Treatment*Inter-Visit Period				0.958	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.163	-0.131	-0.133		
[95% CI]	[-0.203, -0.122]	[-0.171, -0.090]	[-0.190, -0.076]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.089, 0.025] 0.274
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.030 [-0.100, 0.040] 0.407
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.073, 0.068] 0.945

Produced: 17 December 2020 Page 45 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.219	-0.205	-0.189		
[95% CI]	[-0.266, -0.172]	[-0.252, -0.158]	[-0.256, -0.123]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.081, 0.053] 0.679
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.030 [-0.111, 0.052] 0.472
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.016 [-0.066, 0.097] 0.705
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.245	-0.246	-0.231		
[95% CI]	[-0.297, -0.194]	[-0.297, -0.195]	[-0.304, -0.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.072, 0.073] 0.986
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.103, 0.075] 0.756
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.074, 0.103] 0.745

Produced: 17 December 2020 Page 46 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.268	-0.260	-0.248		
[95% CI]	[-0.323, -0.214]	[-0.314, -0.205]	[-0.325, -0.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.086, 0.068] 0.826
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.020 [-0.114, 0.074] 0.674
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.083, 0.106] 0.810
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.269	-0.255	-0.232		
[95% CI]	[-0.325, -0.213]	[-0.311, -0.198]	[-0.312, -0.152]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.014 [-0.094, 0.066] 0.723
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.037 [-0.135, 0.060] 0.454
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.023 [-0.075, 0.121] 0.647

Produced: 17 December 2020 Page 47 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 17.2.12i Statistical Analysis of Average Daily Asthma Symptoms score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average overall night-time asthma symptoms					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.225	-0.216	-0.203		
[95% CI]	[-0.270, -0.179]	[-0.261, -0.170]	[-0.267, -0.139]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.073, 0.055] 0.786
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.100, 0.057] 0.594
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.066, 0.091] 0.757
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.247	-0.236	-0.222		
[95% CI]	[-0.295, -0.199]	[-0.285, -0.188]	[-0.290, -0.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.010 [-0.078, 0.058] 0.771
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.025 [-0.108, 0.058] 0.559
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.069, 0.098] 0.731

Produced: 17 December 2020 Page 48 of 48

Source: Listing 17.2.6.6.1

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

ADDITIONAL_TLF_BATCH3_ASTHMA_SYMPTOM_FREE_DAYS

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch3

Date of Production: 18/12/2020

Identification Code: Additional_TLF_batch3_Asthma_Symptom_Free_Days_CCD-05993AB2-02_20201218(Batch3)

Table 23.2.11a Statistical Analysis of Percentage of Asthma Symptom-Free Days including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.092
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Age Group			0.271
Age Group Treatment Interaction			0.704

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11b Statistical Analysis of Percentage of Asthma Symptom-Free Days including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.115
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Gender			0.348
Gender Treatment Interaction			0.480

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11c Statistical Analysis of Percentage of Asthma Symptom-Free Days including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.054
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
BMI Class			0.562
BMI Class Treatment Interaction			0.334

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11d Statistical Analysis of Percentage of Asthma Symptom-Free Days including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.214
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Smoking Status			0.796
Smoking Status Treatment Interaction			0.749

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11e Statistical Analysis of Percentage of Asthma Symptom-Free Days including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.489
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Number of Exacerbation in the Previous year			0.457
Number of Exacerbation in the Previous year Treatment Interaction			0.052

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11f Statistical Analysis of Percentage of Asthma Symptom-Free Days including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.066
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.279
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Degree of reversibility at screening (delta FEV1)			0.087
Degree of reversibility at screening (delta FEV1) Treatment Interaction			0.063

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11g Statistical Analysis of Percentage of Asthma Symptom-Free Days including Use of Spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.216
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Use of Spacer			0.335
Use of Spacer Treatment Interaction			0.301

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11h Statistical Analysis of Percentage of Asthma Symptom-Free Days including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.086
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Relevant Concomitant Cardiovascular Diseases			0.466
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.177

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.11i Statistical Analysis of Percentage of Asthma Symptom-Free Days including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Symptom-free Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.084
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.282
Baseline			<0.001***
Baseline*Inter-Visit Period			0.010*
Region			0.841
Region Treatment Interaction			0.751

Produced: 18 December 2020, 4:53

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: <65 years old					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	473	446	246		
Effect					
Treatment				0.060	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.444	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.009**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.471	5.109	5.348		
[95% CI]	[4.846, 8.097]	[3.435, 6.783]	[3.094, 7.602]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.363 [-0.971, 3.696] 0.252
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.123 [-1.656, 3.903] 0.428
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.239 [-2.570, 3.048] 0.867

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.813	9.596	10.387		
[95% CI]	[9.513, 14.114]	[7.227, 11.965]	[7.191, 13.583]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.217 [-1.085, 5.519] 0.188
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.426 [-2.511, 5.364] 0.477
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.791 [-3.189, 4.771] 0.697
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.806	12.816	12.704		
[95% CI]	[14.113, 19.499]	[10.045, 15.586]	[8.965, 16.443]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.990 [0.127, 7.854] 0.043*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.102 [-0.505, 8.710] 0.081
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.112 [-4.768, 4.544] 0.962

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.458	15.019	15.053		
[95% CI]	[17.468, 23.447]	[11.944, 18.095]	[10.897, 19.209]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.438 [1.150, 9.727] 0.013*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.405 [0.285, 10.524] 0.039*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.034 [-5.139, 5.206] 0.990
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	21.081	15.804	16.232		
[95% CI]	[17.947, 24.216]	[12.583, 19.024]	[11.873, 20.591]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.278 [0.784, 9.771] 0.021*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.849 [-0.520, 10.218] 0.077
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.429 [-4.993, 5.850] 0.877

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.680	10.639	10.859		
[95% CI]	[11.428, 15.932]	[8.321, 12.958]	[7.732, 13.987]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.040 [-0.192, 6.273] 0.065
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.821 [-1.033, 6.675] 0.151
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.220 [-3.675, 4.115] 0.912
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.213	13.010	13.228		
[95% CI]	[14.699, 19.726]	[10.424, 15.597]	[9.736, 16.721]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.202 [0.595, 7.809] 0.022*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.984 [-0.318, 8.287] 0.070
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.218 [-4.130, 4.566] 0.922

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.713	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.870	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.063	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	5.301	6.036	2.178		
[95% CI]	[1.030, 9.572]	[2.208, 9.864]	[-4.439, 8.795]		
p-value	0.015*	0.002**	0.517		
CHF 5993 pMDI - CHF 1535 pMDI					-0.735 [-6.469, 4.999] 0.801
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.123 [-4.757, 11.003] 0.436
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.858 [-11.507, 3.791] 0.321

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	9.457	7.912	5.161		
[95% CI]	[4.239, 14.675]	[3.237, 12.587]	[-2.947, 13.269]		
p-value	<0.001***	<0.001***	0.211		
CHF 5993 pMDI - CHF 1535 pMDI					1.545 [-5.459, 8.550] 0.664
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.296 [-5.352, 13.944] 0.381
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.751 [-12.116, 6.615] 0.564
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	12.910	11.733	9.692		
[95% CI]	[6.856, 18.963]	[6.285, 17.180]	[0.242, 19.142]		
p-value	<0.001***	<0.001***	0.044*		
CHF 5993 pMDI - CHF 1535 pMDI					1.177 [-6.965, 9.318] 0.776
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.218 [-8.012, 14.447] 0.573
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.041 [-12.956, 8.875] 0.713

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	15.256	14.384	9.278		
[95% CI]	[8.664, 21.847]	[8.437, 20.331]	[-1.061, 19.617]		
p-value	<0.001***	<0.001***	0.078		
CHF 5993 pMDI - CHF 1535 pMDI					0.871 [-8.004, 9.747] 0.847
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.978 [-6.291, 18.247] 0.338
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-5.106 [-17.043, 6.830] 0.400
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	16.786	15.607	13.232		
[95% CI]	[9.996, 23.576]	[9.451, 21.762]	[2.535, 23.929]		
p-value	<0.001***	<0.001***	0.016*		
CHF 5993 pMDI - CHF 1535 pMDI					1.179 [-7.983, 10.341] 0.800
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.554 [-9.123, 16.232] 0.581
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.375 [-14.726, 9.976] 0.705

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12a Statistical Analysis of Percentage of Asthma Symptom-Free Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	10.677	9.681	7.142		
[95% CI]	[5.486, 15.867]	[5.022, 14.339]	[-0.934, 15.218]		
p-value	<0.001***	<0.001***	0.083		
CHF 5993 pMDI - CHF 1535 pMDI					0.996 [-5.977, 7.969] 0.779
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.535 [-6.071, 13.141] 0.469
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.539 [-11.868, 6.791] 0.593
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	13.319	12.315	9.122		
[95% CI]	[7.617, 19.022]	[7.182, 17.447]	[0.218, 18.027]		
p-value	<0.001***	<0.001***	0.045*		
CHF 5993 pMDI - CHF 1535 pMDI					1.005 [-6.665, 8.675] 0.797
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.197 [-6.384, 14.778] 0.435
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.192 [-13.477, 7.093] 0.542

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.036*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.508	
Baseline				0.067	
Baseline*Inter-Visit Period				0.451	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.460	3.312	6.322		
[95% CI]	[4.045, 8.876]	[1.056, 5.568]	[2.858, 9.787]		
p-value	<0.001***	0.004**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.149 [-0.157, 6.454] 0.062
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.138 [-4.086, 4.362] 0.949
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.011 [-1.123, 7.145] 0.153

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.591	7.602	8.994		
[95% CI]	[8.240, 14.943]	[4.469, 10.734]	[4.175, 13.813]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.990 [-0.599, 8.578] 0.088
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.597 [-3.274, 8.468] 0.385
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.393 [-4.355, 7.140] 0.634
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.636	11.006	10.577		
[95% CI]	[12.735, 20.537]	[7.354, 14.658]	[4.973, 16.181]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.630 [0.284, 10.975] 0.039*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.059 [-0.770, 12.888] 0.082
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.429 [-7.118, 6.260] 0.900

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.894	12.902	13.702		
[95% CI]	[16.516, 25.271]	[8.802, 17.002]	[7.401, 20.003]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					7.992 [1.993, 13.991] 0.009**
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.192 [-0.481, 14.864] 0.066
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.800 [-6.717, 8.317] 0.834
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.248	14.024	14.598		
[95% CI]	[17.622, 26.874]	[9.692, 18.355]	[7.936, 21.260]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					8.225 [1.886, 14.563] 0.011*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.650 [-0.461, 15.761] 0.064
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.574 [-7.372, 8.521] 0.887

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.518	8.775	9.435		
[95% CI]	[10.248, 16.789]	[5.717, 11.833]	[4.737, 14.134]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.743 [0.265, 9.222] 0.038*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.083 [-1.643, 9.808] 0.162
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.661 [-4.946, 6.267] 0.817
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.519	11.097	11.776		
[95% CI]	[13.865, 21.172]	[7.678, 14.517]	[6.523, 17.028]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.421 [1.416, 11.426] 0.012*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.743 [-0.655, 12.141] 0.078
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.678 [-5.589, 6.945] 0.832

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	359	325	184		
Effect					
Treatment				0.546	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.612	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.004**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.157	6.737	4.210		
[95% CI]	[4.171, 8.143]	[4.650, 8.823]	[1.438, 6.982]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.580 [-3.462, 2.302] 0.693
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.947 [-1.462, 5.356] 0.263
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.527 [-5.998, 0.944] 0.153

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.300	10.330	10.208		
[95% CI]	[8.586, 14.013]	[7.480, 13.179]	[6.414, 14.003]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.970 [-2.966, 4.906] 0.629
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.091 [-3.572, 5.755] 0.646
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.122 [-4.869, 4.626] 0.960
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.856	13.638	13.387		
[95% CI]	[12.685, 19.027]	[10.309, 16.966]	[8.948, 17.826]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.218 [-2.380, 6.817] 0.344
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.469 [-2.985, 7.923] 0.375
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.251 [-5.801, 5.300] 0.929

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.805	16.270	14.669		
[95% CI]	[15.323, 22.286]	[12.613, 19.927]	[9.785, 19.553]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.534 [-2.517, 7.586] 0.325
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.136 [-1.861, 10.132] 0.176
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.601 [-7.705, 4.503] 0.607
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.233	16.954	16.581		
[95% CI]	[15.619, 22.847]	[13.158, 20.749]	[11.506, 21.657]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.279 [-2.964, 7.522] 0.394
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.652 [-3.578, 8.881] 0.404
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.372 [-6.712, 5.968] 0.908

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12b Statistical Analysis of Percentage of Asthma Symptom-Free Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.962	11.558	10.997		
[95% CI]	[10.292, 15.632]	[8.754, 14.362]	[7.262, 14.732]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.404 [-2.470, 5.277] 0.477
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.965 [-2.626, 6.555] 0.401
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.561 [-5.233, 4.111] 0.814
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	15.982	14.072	13.274		
[95% CI]	[13.017, 18.947]	[10.958, 17.185]	[9.122, 17.427]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.910 [-2.391, 6.211] 0.384
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.708 [-2.393, 7.809] 0.298
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.798 [-5.989, 4.394] 0.763

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: < 25					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.163	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.680	
Baseline				0.007**	
Baseline*Inter-Visit Period				0.050	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.733	4.502	2.315		
[95% CI]	[3.633, 9.832]	[1.530, 7.474]	[-2.136, 6.765]		
p-value	<0.001***	0.003**	0.307		
CHF 5993 pMDI - CHF 1535 pMDI					2.231 [-2.063, 6.524] 0.308
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.418 [-1.011, 9.848] 0.110
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.187 [-7.542, 3.167] 0.422

Produced: 18 December 2020, 4:53

Page 1 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.575	8.794	6.797		
[95% CI]	[7.485, 15.665]	[4.877, 12.710]	[0.932, 12.662]		
p-value	<0.001***	<0.001***	0.023*		
CHF 5993 pMDI - CHF 1535 pMDI					2.781 [-2.881, 8.442] 0.335
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.778 [-2.380, 11.935] 0.190
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.997 [-9.052, 5.058] 0.578
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.632	10.897	9.676		
[95% CI]	[10.873, 20.390]	[6.353, 15.441]	[2.870, 16.483]		
p-value	<0.001***	<0.001***	0.005**		
CHF 5993 pMDI - CHF 1535 pMDI					4.735 [-1.843, 11.313] 0.158
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.955 [-2.357, 14.268] 0.160
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.220 [-9.408, 6.967] 0.770

Produced: 18 December 2020, 4:53

Page 2 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.125	12.347	12.520		
[95% CI]	[14.752, 25.497]	[7.226, 17.469]	[4.811, 20.228]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					7.778 [0.356, 15.199] 0.040*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.605 [-1.799, 17.009] 0.113
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.172 [-9.086, 9.430] 0.971
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.198	14.195	13.426		
[95% CI]	[14.440, 25.955]	[8.713, 19.677]	[5.139, 21.713]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					6.002 [-1.946, 13.951] 0.138
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.772 [-3.327, 16.871] 0.188
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.770 [-10.710, 9.170] 0.879

Produced: 18 December 2020, 4:53

Page 3 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.014	9.266	7.658		
[95% CI]	[8.953, 17.075]	[5.380, 13.151]	[1.839, 13.477]		
p-value	<0.001***	<0.001***	0.010*		
CHF 5993 pMDI - CHF 1535 pMDI					3.748 [-1.871, 9.368] 0.190
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.356 [-1.746, 12.459] 0.139
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.608 [-8.608, 5.392] 0.652
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.586	11.233	10.298		
[95% CI]	[12.031, 21.142]	[6.882, 15.584]	[3.767, 16.829]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					5.353 [-0.945, 11.652] 0.096
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.289 [-1.682, 14.259] 0.122
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.935 [-8.786, 6.915] 0.815

Produced: 18 December 2020, 4:53

Page 4 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: [25-30)					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.255	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.285	
Baseline				0.008**	
Baseline*Inter-Visit Period				0.019*	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.665	6.550	6.208		
[95% CI]	[4.104, 9.226]	[3.896, 9.203]	[2.642, 9.774]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.116 [-3.572, 3.804] 0.951
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.457 [-3.935, 4.849] 0.838
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.341 [-4.786, 4.103] 0.880

Produced: 18 December 2020, 4:53

Page 5 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	12.181	9.400	10.921		
[95% CI]	[8.684, 15.677]	[5.781, 13.019]	[6.009, 15.833]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.781 [-2.251, 7.813] 0.278
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.260 [-4.771, 7.291] 0.682
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.521 [-4.580, 7.622] 0.625
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.590	13.326	14.929		
[95% CI]	[13.410, 21.769]	[8.980, 17.672]	[9.024, 20.833]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.264 [-1.765, 10.294] 0.165
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.661 [-4.575, 9.897] 0.470
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.603 [-5.729, 8.935] 0.668

Produced: 18 December 2020, 4:53

Page 6 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	22.618	16.706	15.482		
[95% CI]	[17.950, 27.286]	[11.836, 21.576]	[8.871, 22.094]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.912 [-0.834, 12.657] 0.086
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.135 [-0.960, 15.231] 0.084
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.224 [-9.435, 6.988] 0.770
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	24.738	17.934	18.157		
[95% CI]	[19.929, 29.546]	[12.914, 22.953]	[11.329, 24.985]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.804 [-0.147, 13.755] 0.055
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.581 [-1.772, 14.934] 0.122
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.223 [-8.252, 8.698] 0.959

Produced: 18 December 2020, 4:53

Page 7 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	14.245	11.075	12.354		
[95% CI]	[10.802, 17.688]	[7.504, 14.646]	[7.511, 17.197]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.170 [-1.791, 8.130] 0.210
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.891 [-4.053, 7.835] 0.532
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.279 [-4.739, 7.296] 0.677
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.921	14.174	14.535		
[95% CI]	[15.016, 22.825]	[10.114, 18.234]	[9.025, 20.046]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.747 [-0.886, 10.379] 0.098
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.385 [-2.370, 11.141] 0.203
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.361 [-6.483, 7.206] 0.917

Produced: 18 December 2020, 4:53

Page 8 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: >=30					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.898	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.713	
Baseline				0.015*	
Baseline*Inter-Visit Period				0.310	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	5.418	4.627	5.667		
[95% CI]	[2.981, 7.854]	[2.186, 7.068]	[2.224, 9.110]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.791 [-2.660, 4.241] 0.653
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.249 [-4.466, 3.967] 0.908
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.040 [-3.183, 5.263] 0.629

Produced: 18 December 2020, 4:53

Page 9 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.403	9.254	10.598		
[95% CI]	[6.911, 13.895]	[5.748, 12.760]	[5.668, 15.528]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.149 [-3.801, 6.100] 0.648
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.195 [-6.235, 5.845] 0.949
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.344 [-4.709, 7.397] 0.663
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.865	13.116	11.528		
[95% CI]	[10.895, 18.834]	[9.134, 17.098]	[5.942, 17.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.749 [-3.876, 7.373] 0.542
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.336 [-3.515, 10.188] 0.339
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.587 [-8.451, 5.277] 0.650

Produced: 18 December 2020, 4:53

Page 10 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	15.836	15.045	14.256		
[95% CI]	[11.588, 20.085]	[10.786, 19.305]	[8.281, 20.231]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.791 [-5.227, 6.809] 0.796
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.580 [-5.750, 8.910] 0.672
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.789 [-8.131, 6.553] 0.833
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	15.524	14.804	15.217		
[95% CI]	[11.117, 19.931]	[10.391, 19.217]	[9.035, 21.399]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.720 [-5.519, 6.960] 0.821
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.307 [-7.283, 7.897] 0.937
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.413 [-7.186, 8.012] 0.915

Produced: 18 December 2020, 4:53

Page 11 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12c Statistical Analysis of Percentage of Asthma Symptom-Free Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.038	10.621	10.340		
[95% CI]	[8.659, 15.418]	[7.230, 14.013]	[5.574, 15.106]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.417 [-3.372, 6.206] 0.561
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.698 [-4.143, 7.539] 0.568
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.281 [-6.133, 5.571] 0.925
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	13.865	12.778	12.520		
[95% CI]	[10.226, 17.505]	[9.126, 16.429]	[7.394, 17.646]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.088 [-4.070, 6.245] 0.679
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.345 [-4.940, 7.630] 0.674
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.258 [-6.554, 6.039] 0.936

Produced: 18 December 2020, 4:53

Page 12 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	488	489	245		
Effect					
Treatment				0.068	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.260	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.007**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.223	5.668	4.779		
[95% CI]	[4.540, 7.907]	[3.987, 7.350]	[2.403, 7.154]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.555 [-1.825, 2.935] 0.647
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.445 [-1.466, 4.356] 0.330
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.890 [-3.801, 2.021] 0.549

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.666	9.831	9.626		
[95% CI]	[9.348, 13.983]	[7.516, 12.146]	[6.348, 12.903]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.835 [-1.441, 5.110] 0.272
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.040 [-1.974, 6.054] 0.319
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.205 [-4.219, 3.808] 0.920
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.873	13.239	12.380		
[95% CI]	[14.183, 19.562]	[10.550, 15.928]	[8.574, 16.185]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.634 [-0.170, 7.437] 0.061
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.493 [-0.167, 9.152] 0.059
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.859 [-5.520, 3.802] 0.718

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.871	15.505	14.687		
[95% CI]	[17.893, 23.850]	[12.527, 18.484]	[10.469, 18.906]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.366 [1.154, 9.579] 0.013*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.184 [1.021, 11.347] 0.019*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.818 [-5.983, 4.348] 0.756
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	21.906	16.839	16.889		
[95% CI]	[18.796, 25.015]	[13.729, 19.949]	[12.481, 21.298]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.066 [0.668, 9.465] 0.024*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.017 [-0.378, 10.411] 0.068
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.050 [-5.347, 5.446] 0.986

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.632	11.026	10.363		
[95% CI]	[11.367, 15.897]	[8.762, 13.289]	[7.160, 13.566]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.607 [-0.596, 5.809] 0.111
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.269 [-0.654, 7.192] 0.102
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.663 [-4.586, 3.261] 0.740
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.491	13.573	13.033		
[95% CI]	[14.971, 20.010]	[11.054, 16.092]	[9.467, 16.600]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.917 [0.354, 7.481] 0.031*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.457 [0.091, 8.823] 0.045*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.540 [-4.908, 3.828] 0.808

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.626	
Inter-Visit Period				0.004**	
Treatment*Inter-Visit Period				0.914	
Baseline				0.375	
Baseline*Inter-Visit Period				0.005**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.645	2.588	6.294		
[95% CI]	[2.968, 10.321]	[-1.185, 6.360]	[1.127, 11.461]		
p-value	<0.001***	0.178	0.017*		
CHF 5993 pMDI - CHF 1535 pMDI					4.057 [-1.216, 9.331] 0.131
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.351 [-5.988, 6.689] 0.913
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.707 [-2.696, 10.110] 0.255

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	9.975	4.846	10.895		
[95% CI]	[5.034, 14.917]	[-0.225, 9.916]	[3.950, 17.840]		
p-value	<0.001***	0.061	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					5.130 [-1.959, 12.218] 0.155
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.920 [-9.439, 7.599] 0.832
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.049 [-2.557, 14.655] 0.167
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	11.814	8.045	12.501		
[95% CI]	[5.790, 17.837]	[1.884, 14.205]	[4.036, 20.966]		
p-value	<0.001***	0.011*	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					3.769 [-4.856, 12.394] 0.390
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.687 [-11.072, 9.697] 0.896
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.456 [-6.022, 14.934] 0.403

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	11.821	10.722	12.134		
[95% CI]	[5.249, 18.392]	[3.992, 17.453]	[2.839, 21.428]		
p-value	<0.001***	0.002**	0.011*		
CHF 5993 pMDI - CHF 1535 pMDI					1.098 [-8.319, 10.515] 0.818
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.313 [-11.692, 11.065] 0.957
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.411 [-10.072, 12.895] 0.809
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	11.005	9.008	9.762		
[95% CI]	[4.210, 17.800]	[2.071, 15.945]	[0.141, 19.382]		
p-value	0.002**	0.011*	0.047**		
CHF 5993 pMDI - CHF 1535 pMDI					1.997 [-7.723, 11.717] 0.686
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.243 [-10.531, 13.018] 0.835
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.754 [-11.114, 12.622] 0.900

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12d Statistical Analysis of Percentage of Asthma Symptom-Free Days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	10.453	6.221	11.052		
[95% CI]	[5.457, 15.449]	[1.101, 11.340]	[4.031, 18.073]		
p-value	<0.001***	0.017*	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					4.232 [-2.929, 11.393] 0.245
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.599 [-9.212, 8.014] 0.891
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.831 [-3.866, 13.528] 0.275
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	10.948	8.076	11.046		
[95% CI]	[5.413, 16.484]	[2.409, 13.743]	[3.248, 18.843]		
p-value	<0.001***	0.005**	0.006**		
CHF 5993 pMDI - CHF 1535 pMDI					2.873 [-5.058, 10.803] 0.476
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.097 [-9.655, 9.461] 0.984
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.970 [-6.677, 12.616] 0.545

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	439	448	229		
Effect					
Treatment				0.069	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.652	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.005**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.663	6.130	3.996		
[95% CI]	[4.909, 8.417]	[4.395, 7.866]	[1.569, 6.424]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.533 [-1.935, 3.001] 0.672
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.667 [-0.328, 5.662] 0.081
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.134 [-5.119, 0.851] 0.161

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.076	9.553	8.075		
[95% CI]	[8.744, 13.409]	[7.243, 11.864]	[4.841, 11.308]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.523 [-1.760, 4.806] 0.363
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.002 [-0.985, 6.989] 0.140
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.479 [-5.453, 2.496] 0.466
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.768	12.376	10.617		
[95% CI]	[13.019, 18.516]	[9.653, 15.099]	[6.805, 14.430]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.392 [-0.477, 7.261] 0.086
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.150 [0.451, 9.850] 0.032*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.758 [-6.444, 2.927] 0.462

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.928	15.119	12.582		
[95% CI]	[15.871, 21.985]	[12.090, 18.149]	[8.330, 16.835]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.809 [-0.495, 8.113] 0.083
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.346 [1.108, 11.583] 0.018*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.537 [-7.759, 2.686] 0.341
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.633	16.195	14.061		
[95% CI]	[16.444, 22.822]	[13.034, 19.356]	[9.619, 18.503]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.437 [-1.053, 7.928] 0.133
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.571 [0.103, 11.040] 0.046*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.134 [-7.587, 3.319] 0.443

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.923	10.546	8.816		
[95% CI]	[10.614, 15.233]	[8.259, 12.834]	[5.615, 12.018]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.377 [-0.874, 5.628] 0.152
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.107 [0.159, 8.055] 0.041*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.730 [-5.666, 2.206] 0.389
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.088	13.081	11.041		
[95% CI]	[13.506, 18.671]	[10.523, 15.639]	[7.456, 14.625]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.007 [-0.628, 6.642] 0.105
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.048 [0.630, 9.465] 0.025*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.041 [-6.445, 2.364] 0.364

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.126	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.670	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.459	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	4.950	2.127	8.708		
[95% CI]	[1.823, 8.077]	[-1.153, 5.407]	[3.991, 13.426]		
p-value	0.002**	0.203	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.823 [-1.709, 7.356] 0.221
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.758 [-9.418, 1.902] 0.192
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.582 [0.836, 12.327] 0.025*

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	12.529	7.823	16.354		
[95% CI]	[7.715, 17.343]	[2.790, 12.856]	[9.060, 23.648]		
p-value	<0.001***	0.002**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.706 [-2.259, 11.671] 0.185
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.825 [-12.564, 4.915] 0.390
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.531 [-0.331, 17.393] 0.059
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.363	13.195	19.225		
[95% CI]	[11.878, 22.848]	[7.459, 18.931]	[10.919, 27.530]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.168 [-3.768, 12.105] 0.302
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.861 [-11.814, 8.092] 0.713
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.029 [-4.065, 16.123] 0.241

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	21.705	13.899	21.116		
[95% CI]	[15.735, 27.675]	[7.640, 20.159]	[12.096, 30.136]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					7.806 [-0.844, 16.456] 0.077
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.589 [-10.227, 11.406] 0.915
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					7.216 [-3.763, 18.196] 0.197
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.724	13.960	22.931		
[95% CI]	[16.447, 29.002]	[7.394, 20.526]	[13.453, 32.408]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					8.765 [-0.319, 17.848] 0.059
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.206 [-11.574, 11.162] 0.972
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.971 [-2.559, 20.501] 0.127

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12e Statistical Analysis of Percentage of Asthma Symptom-Free Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.966	9.839	16.723		
[95% CI]	[9.359, 18.573]	[5.021, 14.658]	[9.748, 23.698]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.127 [-2.540, 10.793] 0.224
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.757 [-11.116, 5.602] 0.517
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.884 [-1.594, 15.362] 0.111
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.071	11.883	19.338		
[95% CI]	[13.017, 23.125]	[6.593, 17.174]	[11.692, 26.985]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.188 [-1.129, 13.504] 0.097
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.268 [-10.433, 7.898] 0.786
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					7.455 [-1.843, 16.753] 0.116

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.289	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.228	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.033*	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	4.102	4.117	5.018		
[95% CI]	[2.206, 5.997]	[2.152, 6.082]	[2.315, 7.720]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.015 [-2.746, 2.716] 0.991
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.916 [-4.216, 2.385] 0.586
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.901 [-2.441, 4.243] 0.597

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1)
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	9.814	8.008	7.963		
[95% CI]	[7.109, 12.520]	[5.198, 10.817]	[4.089, 11.837]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.807 [-2.095, 5.708] 0.364
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.851 [-2.874, 6.576] 0.442
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.045 [-4.832, 4.743] 0.985
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.034	11.112	9.808		
[95% CI]	[10.831, 17.238]	[7.787, 14.437]	[5.216, 14.400]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.922 [-1.695, 7.540] 0.214
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.227 [-1.371, 9.825] 0.139
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.304 [-6.976, 4.367] 0.652

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	17.660	13.517	11.324		
[95% CI]	[14.049, 21.270]	[9.771, 17.264]	[6.143, 16.506]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.142 [-1.062, 9.346] 0.119
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.335 [0.020, 12.650] 0.049*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.193 [-8.590, 4.204] 0.501
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	17.482	13.068	13.600		
[95% CI]	[13.714, 21.251]	[9.158, 16.979]	[8.179, 19.021]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.414 [-1.017, 9.846] 0.111
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.883 [-2.718, 10.484] 0.249
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.532 [-6.155, 7.218] 0.876

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	11.208	9.081	8.503		
[95% CI]	[8.572, 13.843]	[6.345, 11.816]	[4.729, 12.277]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.127 [-1.672, 5.926] 0.272
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.705 [-1.898, 7.307] 0.249
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.577 [-5.241, 4.086] 0.808
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	14.393	11.195	10.439		
[95% CI]	[11.397, 17.389]	[8.086, 14.305]	[6.144, 14.734]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.197 [-1.121, 7.516] 0.146
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.954 [-1.282, 9.190] 0.139
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.756 [-6.061, 4.548] 0.780

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.164	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.694	
Baseline				0.004**	
Baseline*Inter-Visit Period				0.023*	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	8.667	6.391	4.920		
[95% CI]	[6.224, 11.111]	[4.029, 8.753]	[1.521, 8.319]		
p-value	<0.001***	<0.001***	0.005**		
CHF 5993 pMDI - CHF 1535 pMDI					2.277 [-1.122, 5.675] 0.189
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.748 [-0.438, 7.934] 0.079
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.471 [-5.610, 2.668] 0.486

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	13.163	10.314	11.642		
[95% CI]	[9.893, 16.433]	[7.158, 13.470]	[7.093, 16.192]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.849 [-1.696, 7.394] 0.219
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.521 [-4.082, 7.124] 0.594
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.329 [-4.208, 6.866] 0.638
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.506	13.893	15.063		
[95% CI]	[14.736, 22.276]	[10.252, 17.535]	[9.819, 20.307]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.612 [-0.629, 9.854] 0.084
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.443 [-3.016, 9.901] 0.296
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.170 [-5.215, 7.555] 0.719

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	21.724	16.112	17.440		
[95% CI]	[17.615, 25.833]	[12.137, 20.087]	[11.709, 23.171]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.612 [-0.105, 11.329] 0.054
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.284 [-2.767, 11.336] 0.233
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.328 [-5.647, 8.302] 0.709
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	23.595	18.235	18.309		
[95% CI]	[19.306, 27.885]	[14.088, 22.382]	[12.329, 24.290]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.360 [-0.606, 11.327] 0.078
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.286 [-2.074, 12.646] 0.159
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.074 [-7.203, 7.352] 0.984

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12f Statistical Analysis of Percentage of Asthma Symptom-Free Days by Degree of reversibility at screening (delta FEV1)
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.348	11.638	12.450		
[95% CI]	[12.124, 18.572]	[8.524, 14.751]	[7.965, 16.935]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.711 [-0.772, 8.193] 0.105
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.898 [-2.626, 8.422] 0.303
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.812 [-4.648, 6.272] 0.770
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.968	14.365	15.146		
[95% CI]	[15.442, 22.494]	[10.958, 17.772]	[10.237, 20.055]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.603 [-0.300, 9.506] 0.066
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.822 [-2.222, 9.867] 0.215
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.781 [-5.195, 6.757] 0.798

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	129	137	74		
Effect					
Treatment				0.110	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.113	
Baseline				0.008**	
Baseline*Inter-Visit Period				0.357	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	5.854	4.739	7.496		
[95% CI]	[2.514, 9.194]	[1.502, 7.976]	[3.081, 11.911]		
p-value	<0.001***	0.004**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.115 [-3.536, 5.765] 0.638
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.642 [-7.187, 3.903] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.757 [-2.718, 8.232] 0.323

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.262	9.084	14.595		
[95% CI]	[5.669, 14.855]	[4.632, 13.535]	[8.515, 20.675]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.178 [-5.217, 7.574] 0.717
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.333 [-11.966, 3.300] 0.265
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.511 [-2.025, 13.047] 0.151
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.212	11.551	19.195		
[95% CI]	[11.749, 22.674]	[6.257, 16.844]	[11.976, 26.415]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.661 [-1.945, 13.267] 0.144
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.983 [-11.051, 7.085] 0.667
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					7.644 [-1.308, 16.597] 0.094

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	22.364	12.973	21.981		
[95% CI]	[16.356, 28.373]	[7.143, 18.803]	[14.037, 29.925]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					9.391 [1.019, 17.763] 0.028*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.383 [-9.593, 10.360] 0.940
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					9.008 [-0.846, 18.862] 0.073
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.188	13.253	25.383		
[95% CI]	[15.958, 28.418]	[7.203, 19.303]	[17.144, 33.622]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					8.935 [0.252, 17.619] 0.044*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.195 [-13.540, 7.151] 0.544
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					12.130 [1.907, 22.353] 0.020*

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.326	9.744	15.980		
[95% CI]	[8.729, 17.923]	[5.289, 14.198]	[9.900, 22.059]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.582 [-2.818, 9.983] 0.272
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.654 [-10.288, 4.980] 0.495
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.236 [-1.301, 13.773] 0.105
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.805	11.423	19.765		
[95% CI]	[12.702, 22.907]	[6.476, 16.370]	[13.019, 26.512]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.382 [-0.725, 13.488] 0.078
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.961 [-10.433, 6.511] 0.649
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.342 [-0.024, 16.708] 0.051

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.043*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.687	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.003**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.340	5.462	4.153		
[95% CI]	[4.611, 8.069]	[3.712, 7.211]	[1.665, 6.642]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.878 [-1.582, 3.339] 0.484
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.187 [-0.844, 5.217] 0.157
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.308 [-4.351, 1.734] 0.399

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.676	9.225	8.152		
[95% CI]	[9.305, 14.047]	[6.826, 11.625]	[4.731, 11.573]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.451 [-0.923, 5.825] 0.154
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.524 [-0.638, 7.686] 0.097
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.073 [-5.252, 3.105] 0.614
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.741	12.876	10.049		
[95% CI]	[12.995, 18.487]	[10.096, 15.657]	[6.082, 14.015]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.865 [-1.043, 6.774] 0.151
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.693 [0.869, 10.517] 0.021*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.828 [-7.672, 2.016] 0.252

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.686	15.468	11.656		
[95% CI]	[15.642, 21.729]	[12.385, 18.551]	[7.247, 16.064]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.218 [-1.115, 7.551] 0.145
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.030 [1.674, 12.387] 0.010*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.812 [-9.192, 1.567] 0.165
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.712	16.514	12.604		
[95% CI]	[16.527, 22.896]	[13.290, 19.738]	[7.986, 17.222]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.198 [-1.335, 7.730] 0.167
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.108 [1.498, 12.717] 0.013*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.910 [-9.543, 1.723] 0.173

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12g Statistical Analysis of Percentage of Asthma Symptom-Free Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.044	10.612	8.558		
[95% CI]	[10.736, 15.353]	[8.275, 12.949]	[5.226, 11.890]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.432 [-0.854, 5.718] 0.147
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.486 [0.433, 8.539] 0.030*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.054 [-6.124, 2.016] 0.322
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.102	13.281	10.326		
[95% CI]	[13.533, 18.670]	[10.680, 15.882]	[6.613, 14.038]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.820 [-0.836, 6.476] 0.130
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.776 [1.262, 10.290] 0.012*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.956 [-7.489, 1.578] 0.201

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	273	286	134		
Effect					
Treatment				0.854	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.181	
Baseline				0.002**	
Baseline*Inter-Visit Period				0.254	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	4.756	5.478	5.316		
[95% CI]	[2.579, 6.933]	[3.351, 7.605]	[2.206, 8.426]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.722 [-3.766, 2.321] 0.641
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.560 [-4.358, 3.238] 0.772
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.162 [-3.931, 3.606] 0.933

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	8.389	9.222	8.304		
[95% CI]	[5.533, 11.245]	[6.430, 12.014]	[4.232, 12.376]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.833 [-4.826, 3.161] 0.682
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.085 [-4.890, 5.061] 0.973
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.918 [-5.856, 4.020] 0.715
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	12.177	12.023	11.197		
[95% CI]	[8.765, 15.590]	[8.681, 15.365]	[6.330, 16.064]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.155 [-4.621, 4.931] 0.949
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.981 [-4.966, 6.927] 0.746
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.826 [-6.731, 5.079] 0.784

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	16.693	13.065	12.851		
[95% CI]	[12.947, 20.439]	[9.393, 16.738]	[7.507, 18.195]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.628 [-1.618, 8.873] 0.175
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.842 [-2.687, 10.371] 0.248
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.214 [-6.700, 6.271] 0.948
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	16.331	13.474	15.110		
[95% CI]	[12.449, 20.214]	[9.666, 17.282]	[9.580, 20.640]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.857 [-2.581, 8.295] 0.303
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.222 [-5.538, 7.982] 0.723
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.635 [-5.080, 8.351] 0.633

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	9.870	10.154	9.402		
[95% CI]	[7.033, 12.708]	[7.378, 12.930]	[5.355, 13.449]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.284 [-4.253, 3.685] 0.888
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.468 [-4.477, 5.413] 0.853
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.752 [-5.661, 4.157] 0.764
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	13.198	11.704	11.648		
[95% CI]	[10.044, 16.352]	[8.616, 14.793]	[7.150, 16.146]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.494 [-2.920, 5.908] 0.507
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.550 [-3.945, 7.046] 0.580
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-5.514, 5.401] 0.984

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.034*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.351	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.003**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	7.632	5.081	4.672		
[95% CI]	[5.465, 9.798]	[2.856, 7.307]	[1.651, 7.693]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					2.550 [-0.557, 5.657] 0.108
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.960 [-0.759, 6.678] 0.119
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.409 [-4.161, 3.343] 0.830

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.155	9.152	11.089		
[95% CI]	[11.078, 17.232]	[5.994, 12.310]	[6.778, 15.400]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.003 [0.592, 9.413] 0.026*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.066 [-2.231, 8.363] 0.256
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.937 [-3.407, 7.281] 0.477
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	19.736	13.071	13.455		
[95% CI]	[16.213, 23.259]	[9.460, 16.683]	[8.519, 18.390]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.665 [1.618, 11.711] 0.010**
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.281 [0.217, 12.345] 0.042*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.383 [-5.732, 6.499] 0.902

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	22.214	16.645	15.612		
[95% CI]	[18.283, 26.145]	[12.614, 20.676]	[10.082, 21.142]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.570 [-0.062, 11.201] 0.053
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.602 [-0.183, 13.387] 0.056
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.033 [-7.876, 5.810] 0.767
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	24.072	17.956	16.503		
[95% CI]	[19.949, 28.195]	[13.731, 22.180]	[10.684, 22.321]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.116 [0.212, 12.021] 0.042*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.569 [0.438, 14.701] 0.038*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.453 [-8.643, 5.737] 0.692

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12h Statistical Analysis of Percentage of Asthma Symptom-Free Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	16.156	10.636	11.376		
[95% CI]	[13.168, 19.145]	[7.570, 13.703]	[7.191, 15.560]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.520 [1.238, 9.803] 0.012*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.781 [-0.361, 9.923] 0.068
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.739 [-4.448, 5.927] 0.780
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	19.614	13.943	13.699		
[95% CI]	[16.285, 22.943]	[10.529, 17.357]	[9.029, 18.370]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.671 [0.901, 10.441] 0.020*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.915 [0.179, 11.650] 0.043*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.244 [-6.029, 5.541] 0.934

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.129	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.201	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.366	5.019	4.814		
[95% CI]	[4.279, 8.454]	[2.925, 7.113]	[1.866, 7.762]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					1.347 [-1.610, 4.304] 0.371
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.553 [-2.060, 5.165] 0.399
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.205 [-3.822, 3.411] 0.911

Produced: 18 December 2020, 4:53

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.896	8.124	10.805		
[95% CI]	[9.048, 14.745]	[5.267, 10.982]	[6.777, 14.833]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.772 [-0.263, 7.807] 0.067
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.091 [-3.843, 6.025] 0.664
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.681 [-2.259, 7.620] 0.287
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.047	11.909	13.234		
[95% CI]	[12.682, 19.411]	[8.538, 15.280]	[8.476, 17.992]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.138 [-0.625, 8.900] 0.089
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.813 [-3.015, 8.640] 0.344
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.325 [-4.507, 7.157] 0.656

Produced: 18 December 2020, 4:53

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.976	14.196	14.317		
[95% CI]	[16.204, 23.749]	[10.415, 17.977]	[8.972, 19.662]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.781 [0.439, 11.122] 0.034*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.659 [-0.883, 12.202] 0.090
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.121 [-6.426, 6.669] 0.971
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.342	14.680	16.267		
[95% CI]	[16.449, 24.234]	[10.781, 18.578]	[10.747, 21.787]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.662 [0.153, 11.171] 0.044*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.075 [-2.680, 10.829] 0.237
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.587 [-5.171, 8.345] 0.645

Produced: 18 December 2020, 4:53

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.280	9.684	11.191		
[95% CI]	[10.442, 16.118]	[6.838, 12.530]	[7.178, 15.204]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.596 [-0.423, 7.615] 0.079
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.089 [-2.826, 7.004] 0.404
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.507 [-3.413, 6.427] 0.548
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.713	12.052	13.204		
[95% CI]	[13.531, 19.894]	[8.863, 15.240]	[8.703, 17.705]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.661 [0.157, 9.165] 0.043*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.509 [-2.003, 9.021] 0.212
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.152 [-4.364, 6.669] 0.682

Produced: 18 December 2020, 4:53

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
Percentage of Asthma Symptom-free Day					
Number of Patients Included in Model	252	251	127		
Effect					
Treatment				0.381	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.810	
Baseline				0.044*	
Baseline*Inter-Visit Period				0.368	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.122	5.622	5.157		
[95% CI]	[3.851, 8.394]	[3.348, 7.896]	[1.960, 8.353]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					0.500 [-2.715, 3.715] 0.760
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.965 [-2.956, 4.886] 0.629
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.465 [-4.389, 3.459] 0.816

Produced: 18 December 2020, 4:53

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.732	10.534	8.466		
[95% CI]	[7.595, 13.870]	[7.392, 13.676]	[4.037, 12.895]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.198 [-4.243, 4.639] 0.930
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.267 [-3.161, 7.694] 0.412
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.068 [-7.500, 3.363] 0.455
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.179	13.363	11.292		
[95% CI]	[12.573, 19.785]	[9.744, 16.983]	[6.198, 16.385]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.816 [-2.294, 7.926] 0.280
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.887 [-1.353, 11.127] 0.125
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.072 [-8.322, 4.178] 0.515

Produced: 18 December 2020, 4:53

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.969	15.746	14.359		
[95% CI]	[15.055, 22.884]	[11.811, 19.681]	[8.815, 19.904]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.224 [-2.328, 8.775] 0.255
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.610 [-2.176, 11.396] 0.183
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.386 [-8.186, 5.414] 0.689
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.271	17.114	15.405		
[95% CI]	[16.117, 24.424]	[12.939, 21.289]	[9.520, 21.291]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.157 [-2.733, 9.047] 0.293
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.865 [-2.337, 12.068] 0.185
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.708 [-8.926, 5.509] 0.642

Produced: 18 December 2020, 4:53

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 23.2.12i Statistical Analysis of Percentage of Asthma Symptom-Free Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Symptom-free Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.956	11.302	9.478		
[95% CI]	[9.939, 15.973]	[8.277, 14.326]	[5.219, 13.737]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.654 [-2.619, 5.927] 0.447
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.478 [-1.741, 8.696] 0.191
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.823 [-7.048, 3.401] 0.493
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.263	13.840	12.160		
[95% CI]	[12.943, 19.583]	[10.507, 17.172]	[7.468, 16.853]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.423 [-2.281, 7.128] 0.312
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.103 [-1.645, 9.850] 0.161
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.679 [-7.436, 4.077] 0.567

Produced: 18 December 2020, 4:53

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

ADDITIONAL_TLF_BATCH3_PERCENTAGE_OF_ASTHMA_CONTROL_DAYS

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch3

Date of Production: 18/12/2020

Identification Code: Additional_TLF_batch3_Percentage_of_Asthma_Control_Days_CCD-05993AB2-02_20201218(Batch3)

Table 24.2.11a Statistical Analysis of Percentage of Asthma Control Days including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.121
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.353
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Age Group			0.337
Age Group Treatment Interaction			0.514

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11b Statistical Analysis of Percentage of Asthma Control Days including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.212
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.353
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Gender			0.444
Gender Treatment Interaction			0.500

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11c Statistical Analysis of Percentage of Asthma Control Days including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.112
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.354
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
BMI Class			0.604
BMI Class Treatment Interaction			0.311

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11d Statistical Analysis of Percentage of Asthma Control Days including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.394
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.354
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Smoking Status			0.706
Smoking Status Treatment Interaction			0.608

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11e Statistical Analysis of Percentage of Asthma Control Days including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.633
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.353
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Number of Exacerbation in the Previous year			0.550
Number of Exacerbation in the Previous year Treatment Interaction			0.081

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11f Statistical Analysis of Percentage of Asthma Control Days including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.136
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.350
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Degree of reversibility at screening (delta FEV1)			0.120
Degree of reversibility at screening (delta FEV1)			0.082
Treatment Interaction			

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11g Statistical Analysis of Percentage of Asthma Control Days including Use of Spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.416
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.353
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Use of Spacer			0.160
Use of Spacer Treatment Interaction			0.182

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11h Statistical Analysis of Percentage of Asthma Control Days including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.170
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.353
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Relevant Concomitant Cardiovascular Diseases			0.545
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.201

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.11i Statistical Analysis of Percentage of Asthma Control Days including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Asthma Control Day			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.171
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.354
Baseline			<0.001***
Baseline*Inter-Visit Period			0.002**
Region			0.913
Region Treatment Interaction			0.616

Produced: 18 December 2020, 5:05

Page 1 of 1

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: <65 years old					
Percentage of Asthma Control Day					
Number of Patients Included in Model	473	446	246		
Effect					
Treatment				0.084	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.366	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.099	5.043	5.523		
[95% CI]	[4.513, 7.684]	[3.410, 6.675]	[3.325, 7.721]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.056 [-1.220, 3.332] 0.363
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.575 [-2.135, 3.286] 0.677
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.480 [-2.258, 3.219] 0.731

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.118	9.288	10.395		
[95% CI]	[8.865, 13.371]	[6.968, 11.608]	[7.266, 13.524]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.830 [-1.404, 5.064] 0.267
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.723 [-3.133, 4.578] 0.713
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.107 [-2.790, 5.004] 0.577
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.775	11.891	12.586		
[95% CI]	[13.156, 18.393]	[9.197, 14.585]	[8.951, 16.221]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.884 [0.127, 7.641] 0.043*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.189 [-1.291, 7.669] 0.163
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.695 [-3.831, 5.221] 0.763

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.133	13.832	14.668		
[95% CI]	[16.218, 22.048]	[10.833, 16.831]	[10.616, 18.720]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.301 [1.119, 9.484] 0.013*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.465 [-0.527, 9.456] 0.080
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.837 [-4.206, 5.879] 0.745
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.831	14.295	15.967		
[95% CI]	[16.788, 22.873]	[11.169, 17.420]	[11.737, 20.198]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.536 [1.174, 9.898] 0.013*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.863 [-1.348, 9.074] 0.146
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.673 [-3.589, 6.934] 0.533

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.853	10.037	10.825		
[95% CI]	[10.657, 15.049]	[7.776, 12.297]	[7.776, 13.874]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.817 [-0.335, 5.969] 0.080
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.028 [-1.729, 5.785] 0.290
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.789 [-3.008, 4.586] 0.684
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.154	12.041	13.047		
[95% CI]	[13.709, 18.600]	[9.525, 14.557]	[9.650, 16.444]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.113 [0.604, 7.622] 0.022*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.108 [-1.078, 7.293] 0.145
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.006 [-3.223, 5.234] 0.641

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
Percentage of Asthma Control Day					
Number of Patients Included in Model	98	122	41		
Effect					
Treatment				0.734	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.829	
Baseline				0.003**	
Baseline*Inter-Visit Period				0.016*	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	5.672	6.375	2.378		
[95% CI]	[1.549, 9.796]	[2.681, 10.069]	[-4.005, 8.760]		
p-value	0.007**	<0.001***	0.464		
CHF 5993 pMDI - CHF 1535 pMDI					-0.703 [-6.239, 4.833] 0.803
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.294 [-4.310, 10.899] 0.394
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.997 [-11.373, 3.378] 0.287

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	9.508	8.051	5.264		
[95% CI]	[4.449, 14.566]	[3.521, 12.581]	[-2.589, 13.117]		
p-value	<0.001***	<0.001***	0.188		
CHF 5993 pMDI - CHF 1535 pMDI					1.456 [-5.333, 8.246] 0.673
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.243 [-5.105, 13.592] 0.372
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.787 [-11.854, 6.280] 0.546
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	12.381	11.966	9.725		
[95% CI]	[6.475, 18.286]	[6.653, 17.278]	[0.514, 18.936]		
p-value	<0.001***	<0.001***	0.039*		
CHF 5993 pMDI - CHF 1535 pMDI					0.415 [-7.528, 8.357] 0.918
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.656 [-8.294, 13.606] 0.633
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.241 [-12.876, 8.395] 0.679

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	14.298	14.551	9.183		
[95% CI]	[7.871, 20.726]	[8.756, 20.346]	[-0.886, 19.252]		
p-value	<0.001***	<0.001***	0.074		
CHF 5993 pMDI - CHF 1535 pMDI					-0.253 [-8.906, 8.400] 0.954
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.116 [-6.839, 17.070] 0.400
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-5.368 [-16.989, 6.253] 0.364
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	15.944	15.768	13.353		
[95% CI]	[9.330, 22.558]	[9.775, 21.761]	[2.944, 23.762]		
p-value	<0.001***	<0.001***	0.012*		
CHF 5993 pMDI - CHF 1535 pMDI					0.176 [-8.748, 9.100] 0.969
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.592 [-9.750, 14.933] 0.680
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.415 [-14.429, 9.599] 0.693

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12a Statistical Analysis of Percentage of Asthma Control Days by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	10.465	9.901	7.222		
[95% CI]	[5.419, 15.510]	[5.375, 14.428]	[-0.621, 15.065]		
p-value	<0.001***	<0.001***	0.071		
CHF 5993 pMDI - CHF 1535 pMDI					0.563 [-6.214, 7.341] 0.870
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.243 [-6.090, 12.575] 0.494
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.679 [-11.736, 6.378] 0.561
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	12.761	12.507	9.165		
[95% CI]	[7.207, 18.315]	[7.511, 17.503]	[0.501, 17.828]		
p-value	<0.001***	<0.001***	0.038*		
CHF 5993 pMDI - CHF 1535 pMDI					0.254 [-7.215, 7.724] 0.947
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.597 [-6.702, 13.895] 0.492
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.342 [-13.345, 6.661] 0.511

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
Percentage of Asthma Control Day					
Number of Patients Included in Model	212	243	103		
Effect					
Treatment				0.038*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.275	
Baseline				0.027*	
Baseline*Inter-Visit Period				0.072	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.006	3.490	6.176		
[95% CI]	[3.640, 8.371]	[1.281, 5.699]	[2.783, 9.569]		
p-value	<0.001***	0.002**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.515 [-0.722, 5.752] 0.128
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.171 [-4.307, 3.966] 0.935
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.686 [-1.363, 6.734] 0.193

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.635	7.625	8.582		
[95% CI]	[7.344, 13.926]	[4.550, 10.701]	[3.851, 13.314]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.010 [-1.496, 7.515] 0.190
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.052 [-3.712, 7.816] 0.485
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.957 [-4.686, 6.600] 0.739
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.789	10.399	10.153		
[95% CI]	[11.964, 19.615]	[6.817, 13.980]	[4.657, 15.649]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.391 [0.150, 10.632] 0.044*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.637 [-1.060, 12.333] 0.099
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.246 [-6.805, 6.313] 0.941

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.129	11.968	12.786		
[95% CI]	[15.829, 24.428]	[7.942, 15.995]	[6.598, 18.974]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					8.160 [2.269, 14.052] 0.007**
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.343 [-0.193, 14.878] 0.056
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.818 [-6.565, 8.200] 0.828
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	21.791	12.563	14.060		
[95% CI]	[17.255, 26.327]	[8.316, 16.810]	[7.527, 20.593]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					9.228 [3.013, 15.442] 0.004**
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.730 [-0.223, 15.684] 0.057
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.497 [-6.295, 9.289] 0.706

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.698	8.482	9.058		
[95% CI]	[9.485, 15.911]	[5.478, 11.487]	[4.442, 13.674]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.216 [-0.184, 8.615] 0.060
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.640 [-1.984, 9.265] 0.204
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.575 [-4.932, 6.083] 0.837
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.797	10.363	11.216		
[95% CI]	[13.207, 20.387]	[7.002, 13.723]	[6.054, 16.378]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.434 [1.516, 11.353] 0.010*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.581 [-0.707, 11.869] 0.082
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.853 [-5.306, 7.012] 0.786

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
Percentage of Asthma Control Day					
Number of Patients Included in Model	359	325	184		
Effect					
Treatment				0.767	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.675	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.032	6.681	4.503		
[95% CI]	[4.108, 7.957]	[4.659, 8.703]	[1.818, 7.188]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.648 [-3.441, 2.144] 0.649
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.530 [-1.773, 4.832] 0.364
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.178 [-5.540, 1.184] 0.204

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.951	9.999	10.393		
[95% CI]	[8.308, 13.594]	[7.224, 12.775]	[6.698, 14.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.952 [-2.883, 4.786] 0.626
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.558 [-3.984, 5.100] 0.810
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.394 [-4.229, 5.017] 0.867
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.848	12.949	13.403		
[95% CI]	[11.778, 17.918]	[9.727, 16.172]	[9.106, 17.699]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.899 [-2.555, 6.352] 0.403
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.445 [-3.834, 6.725] 0.591
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.453 [-4.919, 5.826] 0.868

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	17.240	15.460	14.567		
[95% CI]	[13.860, 20.619]	[11.910, 19.009]	[9.828, 19.307]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.780 [-3.123, 6.684] 0.476
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.673 [-3.147, 8.492] 0.368
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.892 [-6.816, 5.031] 0.768
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	17.616	16.097	16.468		
[95% CI]	[14.128, 21.104]	[12.435, 19.760]	[11.572, 21.364]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.519 [-3.541, 6.579] 0.556
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.148 [-4.862, 7.158] 0.708
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.371 [-5.746, 6.487] 0.905

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12b Statistical Analysis of Percentage of Asthma Control Days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.293	11.077	11.107		
[95% CI]	[9.704, 14.881]	[8.359, 13.795]	[7.488, 14.727]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.215 [-2.540, 4.971] 0.525
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.185 [-3.264, 5.634] 0.601
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.030 [-4.498, 4.558] 0.990
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	14.853	13.416	13.276		
[95% CI]	[11.986, 17.720]	[10.405, 16.426]	[9.262, 17.290]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.438 [-2.722, 5.597] 0.498
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.577 [-3.355, 6.509] 0.530
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.140 [-5.159, 4.880] 0.956

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Bmi Class: < 25					
Percentage of Asthma Control Day					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.097	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.552	
Baseline				0.017*	
Baseline*Inter-Visit Period				0.036*	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.491	4.542	2.452		
[95% CI]	[3.500, 9.482]	[1.674, 7.410]	[-1.844, 6.747]		
p-value	<0.001***	0.002**	0.262		
CHF 5993 pMDI - CHF 1535 pMDI					1.949 [-2.194, 6.092] 0.355
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.040 [-1.200, 9.279] 0.130
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.090 [-7.257, 3.077] 0.427

Produced: 18 December 2020, 5:05

Page 1 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.164	8.836	6.457		
[95% CI]	[7.235, 15.092]	[5.074, 12.598]	[0.824, 12.090]		
p-value	<0.001***	<0.001***	0.025*		
CHF 5993 pMDI - CHF 1535 pMDI					2.328 [-3.110, 7.765] 0.401
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.707 [-2.168, 11.581] 0.179
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.379 [-9.156, 4.398] 0.490
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.259	9.994	8.815		
[95% CI]	[10.723, 19.794]	[5.662, 14.327]	[2.326, 15.304]		
p-value	<0.001***	<0.001***	0.008**		
CHF 5993 pMDI - CHF 1535 pMDI					5.264 [-1.006, 11.535] 0.100
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.444 [-1.480, 14.368] 0.111
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.180 [-8.985, 6.626] 0.767

Produced: 18 December 2020, 5:05

Page 2 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.887	11.313	11.696		
[95% CI]	[14.677, 25.096]	[6.348, 16.279]	[4.224, 19.169]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					8.573 [1.377, 15.769] 0.020*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					8.190 [-0.926, 17.307] 0.078
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.383 [-8.593, 9.359] 0.933
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.290	12.459	11.991		
[95% CI]	[14.768, 25.812]	[7.202, 17.716]	[4.042, 19.940]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					7.831 [0.208, 15.454] 0.044*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					8.300 [-1.387, 17.986] 0.093
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.468 [-10.003, 9.066] 0.923

Produced: 18 December 2020, 5:05

Page 3 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.650	8.799	7.110		
[95% CI]	[8.767, 16.533]	[5.083, 12.515]	[1.546, 12.675]		
p-value	<0.001***	<0.001***	0.012*		
CHF 5993 pMDI - CHF 1535 pMDI					3.851 [-1.523, 9.224] 0.160
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.540 [-1.252, 12.332] 0.110
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.689 [-8.383, 5.006] 0.620
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.361	10.321	9.471		
[95% CI]	[11.990, 20.733]	[6.146, 14.495]	[3.205, 15.738]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					6.041 [-0.002, 12.084] 0.050
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.890 [-0.757, 14.537] 0.077
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.849 [-8.382, 6.684] 0.825

Produced: 18 December 2020, 5:05

Page 4 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: [25-30)					
Percentage of Asthma Control Day					
Number of Patients Included in Model	217	202	112		
Effect					
Treatment				0.467	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.434	
Baseline				0.002**	
Baseline*Inter-Visit Period				0.001**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.338	6.375	6.189		
[95% CI]	[3.799, 8.876]	[3.746, 9.005]	[2.656, 9.722]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-3.693, 3.618] 0.984
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.149 [-4.205, 4.502] 0.947
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.186 [-4.590, 4.217] 0.934

Produced: 18 December 2020, 5:05

Page 5 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.067	8.808	10.870		
[95% CI]	[7.637, 14.497]	[5.258, 12.357]	[6.053, 15.687]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.259 [-2.677, 7.196] 0.369
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.197 [-5.719, 6.113] 0.948
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.062 [-3.920, 8.045] 0.499
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.735	12.634	14.834		
[95% CI]	[11.645, 19.826]	[8.381, 16.887]	[9.057, 20.612]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.102 [-2.800, 9.003] 0.302
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.901 [-6.181, 7.984] 0.803
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.200 [-4.973, 9.374] 0.547

Produced: 18 December 2020, 5:05

Page 6 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.093	15.653	15.240		
[95% CI]	[15.542, 24.643]	[10.906, 20.400]	[8.796, 21.683]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.440 [-2.136, 11.016] 0.185
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.853 [-3.038, 12.745] 0.228
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.414 [-8.416, 7.589] 0.919
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.350	16.797	17.920		
[95% CI]	[17.654, 27.047]	[11.895, 21.699]	[11.252, 24.589]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.553 [-1.236, 12.342] 0.109
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.430 [-3.729, 12.590] 0.287
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.123 [-7.153, 9.399] 0.790

Produced: 18 December 2020, 5:05

Page 7 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.853	10.494	12.284		
[95% CI]	[9.475, 16.232]	[6.990, 13.997]	[7.534, 17.035]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.359 [-2.508, 7.227] 0.341
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.569 [-5.263, 6.401] 0.848
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.791 [-4.111, 7.693] 0.551
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.994	13.337	14.381		
[95% CI]	[13.183, 20.805]	[9.375, 17.300]	[9.003, 19.758]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.657 [-1.842, 9.155] 0.192
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.613 [-3.981, 9.207] 0.437
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.043 [-5.636, 7.722] 0.759

Produced: 18 December 2020, 5:05

Page 8 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Bmi Class: >=30					
Percentage of Asthma Control Day					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.923	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.647	
Baseline				0.020*	
Baseline*Inter-Visit Period				0.077	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	5.264	4.897	5.938		
[95% CI]	[2.934, 7.594]	[2.562, 7.232]	[2.646, 9.230]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.367 [-2.933, 3.667] 0.827
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.674 [-4.707, 3.358] 0.743
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.041 [-2.996, 5.079] 0.613

Produced: 18 December 2020, 5:05

Page 9 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.343	9.287	10.726		
[95% CI]	[6.910, 13.775]	[5.841, 12.733]	[5.881, 15.571]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.056 [-3.810, 5.921] 0.670
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.383 [-6.319, 5.553] 0.899
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.439 [-4.509, 7.386] 0.635
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.537	12.695	11.739		
[95% CI]	[10.654, 18.421]	[8.800, 16.590]	[6.275, 17.204]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.842 [-3.661, 7.345] 0.511
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.798 [-3.905, 9.500] 0.413
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.956 [-7.669, 5.758] 0.780

Produced: 18 December 2020, 5:05

Page 10 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	15.271	14.461	13.912		
[95% CI]	[11.109, 19.432]	[10.289, 18.633]	[8.060, 19.763]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.810 [-5.085, 6.705] 0.787
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.359 [-5.820, 8.538] 0.710
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.549 [-7.738, 6.640] 0.881
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	14.797	14.184	15.634		
[95% CI]	[10.497, 19.097]	[9.879, 18.490]	[9.603, 21.664]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.613 [-5.475, 6.700] 0.843
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.837 [-8.242, 6.568] 0.824
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.449 [-5.963, 8.862] 0.701

Produced: 18 December 2020, 5:05

Page 11 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12c Statistical Analysis of Percentage of Asthma Control Days by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	11.820	10.447	10.535		
[95% CI]	[8.515, 15.125]	[7.131, 13.763]	[5.875, 15.195]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.373 [-3.311, 6.057] 0.565
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.285 [-4.427, 6.997] 0.659
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.088 [-5.634, 5.810] 0.976
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	13.436	12.390	12.621		
[95% CI]	[9.873, 16.999]	[8.816, 15.964]	[7.604, 17.637]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.046 [-4.003, 6.095] 0.684
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.815 [-5.336, 6.967] 0.795
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.231 [-5.931, 6.392] 0.941

Produced: 18 December 2020, 5:05

Page 12 of 12

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
Percentage of Asthma Control Day					
Number of Patients Included in Model	488	489	245		
Effect					
Treatment				0.112	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.349	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.016	5.554	4.836		
[95% CI]	[4.370, 7.663]	[3.910, 7.199]	[2.513, 7.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.462 [-1.865, 2.790] 0.697
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.181 [-1.666, 4.028] 0.416
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.719 [-3.565, 2.128] 0.620

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.047	9.450	9.562		
[95% CI]	[8.778, 13.316]	[7.184, 11.716]	[6.353, 12.770]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.597 [-1.610, 4.805] 0.329
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.485 [-2.444, 5.414] 0.458
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.112 [-3.817, 4.041] 0.955
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.802	12.398	12.196		
[95% CI]	[13.181, 18.423]	[9.778, 15.018]	[8.488, 15.904]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.404 [-0.303, 7.111] 0.072
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.606 [-0.934, 8.147] 0.119
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.202 [-4.744, 4.340] 0.930

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.435	14.451	14.382		
[95% CI]	[16.523, 22.347]	[11.539, 17.363]	[10.259, 18.506]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.984 [0.865, 9.103] 0.018*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.053 [0.005, 10.100] 0.050*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.069 [-5.118, 4.981] 0.979
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.546	15.616	16.493		
[95% CI]	[17.521, 23.571]	[12.591, 18.641]	[12.205, 20.781]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.930 [0.651, 9.209] 0.024*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.053 [-1.194, 9.300] 0.130
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.877 [-4.372, 6.126] 0.743

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.834	10.438	10.253		
[95% CI]	[10.622, 15.045]	[8.228, 12.648]	[7.125, 13.381]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.395 [-0.732, 5.523] 0.133
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.580 [-1.250, 6.411] 0.187
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.185 [-4.016, 3.646] 0.925
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.391	12.714	12.805		
[95% CI]	[13.934, 18.847]	[10.258, 15.169]	[9.329, 16.281]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.677 [0.203, 7.151] 0.038*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.586 [-0.670, 7.842] 0.099
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.091 [-4.166, 4.349] 0.966

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Percentage of Asthma Control Day					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.663	
Inter-Visit Period				0.005**	
Treatment*Inter-Visit Period				0.845	
Baseline				0.909	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.179	3.532	7.010		
[95% CI]	[2.794, 9.563]	[0.060, 7.004]	[2.250, 11.770]		
p-value	<0.001***	0.046*	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					2.647 [-2.204, 7.497] 0.283
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.831 [-6.670, 5.007] 0.779
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.478 [-2.418, 9.374] 0.246

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	9.688	5.777	11.263		
[95% CI]	[4.986, 14.390]	[0.954, 10.601]	[4.650, 17.876]		
p-value	<0.001***	0.019*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.911 [-2.828, 10.650] 0.254
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.575 [-9.686, 6.537] 0.702
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.486 [-2.705, 13.677] 0.188
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	11.638	8.383	12.826		
[95% CI]	[5.879, 17.396]	[2.495, 14.272]	[4.728, 20.925]		
p-value	<0.001***	0.005**	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					3.254 [-4.986, 11.494] 0.437
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.189 [-11.124, 8.746] 0.814
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.443 [-5.577, 14.464] 0.383

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	11.650	10.813	11.387		
[95% CI]	[5.369, 17.931]	[4.384, 17.243]	[2.499, 20.276]		
p-value	<0.001***	0.001**	0.012*		
CHF 5993 pMDI - CHF 1535 pMDI					0.837 [-8.155, 9.828] 0.855
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.262 [-10.619, 11.143] 0.962
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.574 [-10.404, 11.552] 0.918
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	10.905	8.307	10.501		
[95% CI]	[4.368, 17.441]	[1.634, 14.979]	[1.243, 19.759]		
p-value	0.001**	0.015*	0.026*		
CHF 5993 pMDI - CHF 1535 pMDI					2.598 [-6.746, 11.941] 0.584
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.404 [-10.927, 11.735] 0.944
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.194 [-9.225, 13.613] 0.705

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12d Statistical Analysis of Percentage of Asthma Control Days by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	10.198	6.835	11.450		
[95% CI]	[5.454, 14.942]	[1.976, 11.695]	[4.779, 18.122]		
p-value	<0.001***	0.006**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.363 [-3.431, 10.157] 0.330
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.253 [-9.436, 6.931] 0.763
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.615 [-3.644, 12.875] 0.272
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	10.752	8.246	11.214		
[95% CI]	[5.460, 16.044]	[2.830, 13.662]	[3.756, 18.673]		
p-value	<0.001***	0.003**	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					2.506 [-5.069, 10.081] 0.515
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.462 [-9.605, 8.680] 0.921
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.969 [-6.256, 12.193] 0.526

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Percentage of Asthma Control Day					
Number of Patients Included in Model	439	448	229		
Effect					
Treatment				0.150	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.726	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.387	6.204	4.237		
[95% CI]	[4.679, 8.094]	[4.515, 7.893]	[1.875, 6.600]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.182 [-2.219, 2.584] 0.882
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.149 [-0.765, 5.063] 0.148
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.967 [-4.871, 0.938] 0.184

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.605	9.459	8.053		
[95% CI]	[8.319, 12.890]	[7.195, 11.723]	[4.886, 11.221]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.145 [-2.072, 4.363] 0.485
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.551 [-1.354, 6.457] 0.200
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.406 [-5.300, 2.488] 0.479
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.879	11.943	10.605		
[95% CI]	[12.200, 17.558]	[9.289, 14.597]	[6.889, 14.320]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.936 [-0.836, 6.708] 0.127
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.274 [-0.306, 8.854] 0.067
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.338 [-5.905, 3.229] 0.565

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	17.725	14.560	12.445		
[95% CI]	[14.731, 20.720]	[11.593, 17.527]	[8.280, 16.609]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.165 [-1.051, 7.382] 0.141
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.280 [0.152, 10.409] 0.044*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.115 [-7.230, 2.999] 0.417
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	18.472	15.404	14.071		
[95% CI]	[15.355, 21.589]	[12.314, 18.493]	[9.729, 18.412]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.068 [-1.321, 7.458] 0.170
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.401 [-0.942, 9.745] 0.106
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.333 [-6.662, 3.996] 0.624

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.257	10.296	8.840		
[95% CI]	[10.005, 14.510]	[8.065, 12.527]	[5.718, 11.962]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.961 [-1.210, 5.132] 0.225
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.417 [-0.433, 7.267] 0.082
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.456 [-5.294, 2.382] 0.457
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	15.164	12.623	11.018		
[95% CI]	[12.642, 17.685]	[10.124, 15.121]	[7.517, 14.518]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.541 [-1.010, 6.091] 0.161
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.146 [-0.168, 8.460] 0.060
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.605 [-5.906, 2.696] 0.464

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Percentage of Asthma Control Day					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.077	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.487	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.334	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	4.791	2.059	8.453		
[95% CI]	[1.758, 7.824]	[-1.122, 5.240]	[3.877, 13.028]		
p-value	0.002**	0.204	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.732 [-1.664, 7.127] 0.222
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.662 [-9.151, 1.828] 0.190
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.393 [0.820, 11.966] 0.025*

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.609	7.311	16.347		
[95% CI]	[6.952, 16.265]	[2.443, 12.179]	[9.293, 23.402]		
p-value	<0.001***	0.003**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.298 [-2.439, 11.034] 0.210
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.739 [-13.191, 3.714] 0.271
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					9.036 [0.465, 17.607] 0.039*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.200	11.706	18.621		
[95% CI]	[10.902, 21.497]	[6.167, 17.244]	[10.597, 26.645]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.494 [-3.171, 12.158] 0.250
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.422 [-12.037, 7.193] 0.621
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.916 [-2.835, 16.666] 0.164

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.223	11.842	19.786		
[95% CI]	[14.486, 25.959]	[5.829, 17.856]	[11.116, 28.455]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					8.380 [0.069, 16.691] 0.048*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.437 [-9.959, 10.833] 0.934
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					7.943 [-2.608, 18.494] 0.140
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	21.488	11.558	21.688		
[95% CI]	[15.518, 27.458]	[5.315, 17.801]	[12.672, 30.703]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					9.930 [1.292, 18.567] 0.024*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.200 [-11.013, 10.613] 0.971
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					10.130 [-0.836, 21.095] 0.070

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12e Statistical Analysis of Percentage of Asthma Control Days by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.032	8.869	16.357		
[95% CI]	[8.567, 17.496]	[4.201, 13.538]	[9.597, 23.117]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.162 [-2.297, 10.622] 0.206
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.325 [-11.427, 4.776] 0.420
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					7.488 [-0.728, 15.703] 0.074
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.919	10.290	18.510		
[95% CI]	[12.067, 21.771]	[5.212, 15.368]	[11.167, 25.854]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.629 [-0.395, 13.652] 0.064
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.591 [-10.393, 7.211] 0.722
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.220 [-0.708, 17.148] 0.071

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL Percentage of Asthma Control Day					
Number of Patients Included in Model	299	278	147		
Effect					
Treatment				0.346	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.250	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.006**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	4.118	4.325	5.125		
[95% CI]	[2.270, 5.965]	[2.410, 6.241]	[2.491, 7.758]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.208 [-2.870, 2.455] 0.878
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.007 [-4.223, 2.209] 0.539
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.800 [-2.458, 4.057] 0.630

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	9.541	8.049	7.975		
[95% CI]	[6.886, 12.196]	[5.291, 10.806]	[4.174, 11.776]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.492 [-2.336, 5.321] 0.444
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.566 [-3.069, 6.201] 0.507
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.073 [-4.771, 4.624] 0.976
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	13.446	10.506	9.704		
[95% CI]	[10.339, 16.552]	[7.282, 13.730]	[5.252, 14.156]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.940 [-1.539, 7.418] 0.198
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.741 [-1.686, 9.169] 0.176
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.802 [-6.301, 4.698] 0.775

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	16.564	12.679	11.108		
[95% CI]	[13.043, 20.086]	[9.024, 16.333]	[6.055, 16.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.886 [-1.191, 8.963] 0.133
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.457 [-0.701, 11.614] 0.082
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.571 [-7.810, 4.668] 0.621
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	16.283	11.845	13.185		
[95% CI]	[12.644, 19.923]	[8.069, 15.622]	[7.951, 18.419]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.438 [-0.808, 9.685] 0.097
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.098 [-3.275, 9.472] 0.340
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.340 [-5.118, 7.797] 0.684

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	10.809	8.799	8.468		
[95% CI]	[8.243, 13.376]	[6.134, 11.464]	[4.793, 12.142]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.010 [-1.690, 5.711] 0.287
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.341 [-2.139, 6.822] 0.305
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.331 [-4.872, 4.210] 0.886
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	13.622	10.547	10.267		
[95% CI]	[10.712, 16.532]	[7.526, 13.567]	[6.096, 14.438]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.075 [-1.119, 7.270] 0.150
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.355 [-1.729, 8.439] 0.196
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.279 [-5.431, 4.872] 0.915

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL Percentage of Asthma Control Day					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.238	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.703	
Baseline				0.003**	
Baseline*Inter-Visit Period				0.002**	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	8.141	6.265	5.091		
[95% CI]	[5.767, 10.515]	[3.970, 8.560]	[1.789, 8.394]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					1.876 [-1.426, 5.178] 0.265
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.050 [-1.018, 7.117] 0.141
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.174 [-5.195, 2.848] 0.567

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	12.264	9.907	11.582		
[95% CI]	[9.080, 15.448]	[6.834, 12.979]	[7.153, 16.012]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.357 [-2.068, 6.782] 0.296
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.681 [-4.774, 6.137] 0.806
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.676 [-3.715, 7.067] 0.542
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.173	13.180	14.890		
[95% CI]	[13.495, 20.850]	[9.627, 16.732]	[9.774, 20.005]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.993 [-1.120, 9.107] 0.126
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.283 [-4.017, 8.584] 0.477
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.710 [-4.518, 7.939] 0.590

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.285	15.206	16.887		
[95% CI]	[16.279, 24.291]	[11.331, 19.081]	[11.300, 22.474]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.079 [-0.494, 10.653] 0.074
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.398 [-3.477, 10.273] 0.332
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.681 [-5.119, 8.481] 0.628
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.442	17.189	18.226		
[95% CI]	[18.260, 26.625]	[13.145, 21.232]	[12.394, 24.058]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.254 [-0.564, 11.071] 0.077
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.216 [-2.960, 11.393] 0.249
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.038 [-6.059, 8.134] 0.774

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12f Statistical Analysis of Percentage of Asthma Control Days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	14.273	11.109	12.365		
[95% CI]	[11.131, 17.415]	[8.075, 14.143]	[7.994, 16.735]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.164 [-1.204, 7.532] 0.155
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.908 [-3.475, 7.291] 0.487
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.256 [-4.065, 6.577] 0.643
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.777	13.615	14.935		
[95% CI]	[14.342, 21.211]	[10.296, 16.933]	[10.153, 19.716]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.162 [-0.614, 8.938] 0.088
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.842 [-3.045, 8.729] 0.344
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.320 [-4.501, 7.140] 0.656

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
Percentage of Asthma Control Day					
Number of Patients Included in Model	129	137	74		
Effect					
Treatment				0.078	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.063	
Baseline				0.026*	
Baseline*Inter-Visit Period				0.111	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	5.896	5.074	8.280		
[95% CI]	[2.646, 9.146]	[1.923, 8.224]	[3.987, 12.573]		
p-value	<0.001***	0.002**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.822 [-3.704, 5.348] 0.721
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.384 [-7.774, 3.006] 0.385
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.206 [-2.119, 8.531] 0.237

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.304	9.279	14.745		
[95% CI]	[5.848, 14.759]	[4.960, 13.598]	[8.851, 20.639]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.025 [-5.181, 7.231] 0.746
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.441 [-11.838, 2.956] 0.238
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.466 [-1.841, 12.773] 0.142
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.578	11.256	19.127		
[95% CI]	[11.295, 21.861]	[6.135, 16.377]	[12.149, 26.105]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.322 [-2.037, 12.680] 0.156
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.549 [-11.311, 6.213] 0.568
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					7.871 [-0.783, 16.525] 0.075

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	21.679	12.109	21.514		
[95% CI]	[15.856, 27.503]	[6.457, 17.761]	[13.820, 29.207]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					9.570 [1.454, 17.687] 0.021*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.166 [-9.493, 9.825] 0.973
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					9.405 [-0.140, 18.950] 0.053
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	21.728	12.368	25.675		
[95% CI]	[15.671, 27.785]	[6.483, 18.252]	[17.671, 33.679]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					9.361 [0.916, 17.805] 0.030*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.947 [-13.995, 6.101] 0.440
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					13.307 [3.373, 23.241] 0.009**

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	13.004	9.697	16.110		
[95% CI]	[8.559, 17.449]	[5.388, 14.005]	[10.236, 21.984]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.307 [-2.883, 9.498] 0.294
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.106 [-10.480, 4.269] 0.408
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.413 [-0.871, 13.698] 0.084
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.353	10.963	19.772		
[95% CI]	[12.418, 22.288]	[6.177, 15.748]	[13.252, 26.292]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.390 [-0.484, 13.265] 0.068
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.419 [-10.605, 5.767] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.810 [0.722, 16.897] 0.033*

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
Percentage of Asthma Control Day					
Number of Patients Included in Model	442	431	213		
Effect					
Treatment				0.083	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.781	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.038	5.404	4.022		
[95% CI]	[4.358, 7.719]	[3.703, 7.105]	[1.603, 6.441]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.635 [-1.757, 3.027] 0.603
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.016 [-0.929, 4.962] 0.179
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.382 [-4.339, 1.576] 0.360

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	10.957	8.910	8.020		
[95% CI]	[8.636, 13.278]	[6.561, 11.259]	[4.672, 11.369]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.047 [-1.256, 5.350] 0.224
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.936 [-1.137, 7.010] 0.158
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.890 [-4.980, 3.201] 0.670
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.735	12.097	9.842		
[95% CI]	[12.059, 17.411]	[9.387, 14.807]	[5.977, 13.707]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.639 [-1.171, 6.448] 0.174
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.893 [0.192, 9.594] 0.041*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.254 [-6.975, 2.466] 0.349

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	17.283	14.581	11.273		
[95% CI]	[14.311, 20.255]	[11.570, 17.591]	[6.969, 15.577]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.702 [-1.530, 6.934] 0.211
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.010 [0.779, 11.240] 0.024*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.308 [-8.561, 1.945] 0.217
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	18.338	15.305	12.140		
[95% CI]	[15.249, 21.427]	[12.178, 18.433]	[7.661, 16.619]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.033 [-1.364, 7.430] 0.176
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					6.198 [0.757, 11.639] 0.026*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-3.165 [-8.628, 2.298] 0.256

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12g Statistical Analysis of Percentage of Asthma Control Days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.235	10.086	8.386		
[95% CI]	[9.981, 14.489]	[7.804, 12.368]	[5.134, 11.639]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.148 [-1.060, 5.357] 0.189
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.848 [-0.109, 7.805] 0.057
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.700 [-5.674, 2.273] 0.401
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	15.002	12.501	10.030		
[95% CI]	[12.500, 17.505]	[9.967, 15.035]	[6.413, 13.646]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.501 [-1.061, 6.064] 0.169
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.973 [0.575, 9.370] 0.027*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.471 [-6.888, 1.945] 0.273

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Percentage of Asthma Control Day					
Number of Patients Included in Model	273	286	134		
Effect					
Treatment				0.909	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.333	
Baseline				0.003**	
Baseline*Inter-Visit Period				0.056	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	4.702	5.511	5.389		
[95% CI]	[2.610, 6.795]	[3.466, 7.556]	[2.399, 8.378]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.809 [-3.735, 2.117] 0.588
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.686 [-4.336, 2.964] 0.712
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.123 [-3.746, 3.501] 0.947

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	8.292	8.900	8.220		
[95% CI]	[5.518, 11.066]	[6.187, 11.612]	[4.265, 12.175]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.608 [-4.488, 3.271] 0.758
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.072 [-4.760, 4.903] 0.977
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.680 [-5.477, 4.117] 0.781
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	11.811	11.433	11.305		
[95% CI]	[8.480, 15.142]	[8.170, 14.696]	[6.554, 16.056]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.378 [-4.285, 5.041] 0.874
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.506 [-5.298, 6.310] 0.864
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.128 [-5.894, 5.638] 0.965

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	15.517	12.500	12.797		
[95% CI]	[11.879, 19.155]	[8.933, 16.068]	[7.607, 17.987]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.016 [-2.079, 8.111] 0.245
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.720 [-3.619, 9.059] 0.400
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.296 [-6.003, 6.596] 0.926
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	15.095	12.765	15.232		
[95% CI]	[11.332, 18.858]	[9.074, 16.457]	[9.872, 20.591]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.329 [-2.942, 7.601] 0.386
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.137 [-6.687, 6.413] 0.967
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.466 [-4.043, 8.976] 0.457

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	9.634	9.742	9.445		
[95% CI]	[6.873, 12.396]	[7.041, 12.444]	[5.507, 13.384]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.108 [-3.971, 3.755] 0.956
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.189 [-4.622, 5.000] 0.939
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.297 [-5.075, 4.481] 0.903
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	12.478	11.183	11.683		
[95% CI]	[9.419, 15.537]	[8.186, 14.179]	[7.320, 16.046]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.296 [-2.986, 5.577] 0.553
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.795 [-4.534, 6.125] 0.770
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.500 [-4.794, 5.795] 0.853

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Percentage of Asthma Control Day					
Number of Patients Included in Model	298	282	153		
Effect					
Treatment				0.056	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.341	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	7.229	5.125	4.845		
[95% CI]	[5.101, 9.357]	[2.939, 7.311]	[1.878, 7.812]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					2.104 [-0.948, 5.155] 0.176
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.384 [-1.268, 6.035] 0.200
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.280 [-3.965, 3.405] 0.881

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	13.150	9.102	11.110		
[95% CI]	[10.131, 16.170]	[6.003, 12.201]	[6.880, 15.341]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.048 [-0.280, 8.376] 0.067
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.040 [-3.158, 7.238] 0.441
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.008 [-3.236, 7.252] 0.452
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.259	12.344	13.093		
[95% CI]	[14.840, 21.679]	[8.838, 15.850]	[8.301, 17.884]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.915 [1.016, 10.814] 0.018*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.167 [-0.721, 11.054] 0.085
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.748 [-5.188, 6.685] 0.805

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.878	15.463	14.914		
[95% CI]	[17.033, 24.722]	[11.521, 19.405]	[9.505, 20.322]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.414 [-0.094, 10.922] 0.054
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.964 [-0.672, 12.600] 0.078
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.550 [-7.242, 6.142] 0.872
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.941	16.412	15.921		
[95% CI]	[18.930, 26.951]	[12.303, 20.520]	[10.260, 21.581]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.529 [0.786, 12.272] 0.026*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					7.020 [0.082, 13.958] 0.047*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.491 [-7.485, 6.503] 0.890

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12h Statistical Analysis of Percentage of Asthma Control Days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	14.990	10.236	11.214		
[95% CI]	[12.075, 17.905]	[7.245, 13.227]	[7.132, 15.295]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.754 [0.577, 8.932] 0.026*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.777 [-1.239, 8.792] 0.140
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.978 [-4.082, 6.038] 0.705
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.410	13.069	13.296		
[95% CI]	[15.164, 21.656]	[9.739, 16.398]	[8.742, 17.851]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.342 [0.690, 9.993] 0.024*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.114 [-0.479, 10.707] 0.073
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.228 [-5.414, 5.869] 0.937

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
Percentage of Asthma Control Day					
Number of Patients Included in Model	319	317	160		
Effect					
Treatment				0.133	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.227	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.334	5.007	4.913		
[95% CI]	[4.301, 8.367]	[2.968, 7.047]	[2.042, 7.783]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.326 [-1.554, 4.206] 0.366
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.421 [-2.096, 4.939] 0.428
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.095 [-3.617, 3.427] 0.958

Produced: 18 December 2020, 5:05

Page 1 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	11.810	7.824	10.680		
[95% CI]	[9.041, 14.578]	[5.046, 10.601]	[6.765, 14.596]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.986 [0.064, 7.907] 0.046*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.129 [-3.666, 5.924] 0.644
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.856 [-1.945, 7.658] 0.243
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	15.404	11.367	12.855		
[95% CI]	[12.123, 18.685]	[8.079, 14.655]	[8.214, 17.496]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.037 [-0.608, 8.683] 0.088
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.549 [-3.134, 8.233] 0.379
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.488 [-4.201, 7.177] 0.608

Produced: 18 December 2020, 5:05

Page 2 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.838	13.375	13.943		
[95% CI]	[15.155, 22.521]	[9.684, 17.067]	[8.725, 19.161]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.463 [0.248, 10.677] 0.040*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					4.895 [-1.492, 11.281] 0.133
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.568 [-5.825, 6.961] 0.862
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.150	13.728	15.801		
[95% CI]	[15.356, 22.943]	[9.929, 17.527]	[10.422, 21.181]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.422 [0.053, 10.791] 0.048*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.348 [-3.234, 9.930] 0.318
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.073 [-4.514, 8.660] 0.537

Produced: 18 December 2020, 5:05

Page 3 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.903	9.298	10.964		
[95% CI]	[10.140, 15.665]	[6.528, 12.069]	[7.057, 14.871]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.604 [-0.308, 7.517] 0.071
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.939 [-2.846, 6.724] 0.427
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.665 [-3.125, 6.456] 0.495
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	15.942	11.418	12.882		
[95% CI]	[12.843, 19.042]	[8.311, 14.525]	[8.496, 17.269]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.524 [0.135, 8.913] 0.043*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.060 [-2.311, 8.431] 0.264
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.464 [-3.912, 6.840] 0.593

Produced: 18 December 2020, 5:05

Page 4 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
Percentage of Asthma Control Day					
Number of Patients Included in Model	252	251	127		
Effect					
Treatment				0.613	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.610	
Baseline				0.025*	
Baseline*Inter-Visit Period				0.085	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	5.617	5.716	5.354		
[95% CI]	[3.413, 7.820]	[3.510, 7.922]	[2.254, 8.455]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.099 [-3.218, 3.019] 0.950
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.263 [-3.541, 4.066] 0.892
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.362 [-4.167, 3.443] 0.852

Produced: 18 December 2020, 5:05

Page 5 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	9.564	10.471	8.581		
[95% CI]	[6.482, 12.647]	[7.385, 13.557]	[4.232, 12.931]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.906 [-5.269, 3.456] 0.683
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.983 [-4.348, 6.314] 0.717
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.889 [-7.223, 3.444] 0.487
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.859	12.526	11.489		
[95% CI]	[11.362, 18.355]	[9.017, 16.035]	[6.552, 16.426]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.333 [-2.622, 7.287] 0.356
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.369 [-2.680, 9.419] 0.274
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.037 [-7.094, 5.021] 0.737

Produced: 18 December 2020, 5:05

Page 6 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	17.563	14.760	14.003		
[95% CI]	[13.753, 21.374]	[10.930, 18.590]	[8.608, 19.399]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.804 [-2.600, 8.207] 0.309
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.560 [-3.045, 10.165] 0.290
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.756 [-7.373, 5.860] 0.822
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.104	15.716	15.490		
[95% CI]	[15.088, 23.119]	[11.680, 19.751]	[9.801, 21.179]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.388 [-2.306, 9.082] 0.243
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.613 [-3.350, 10.576] 0.309
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.225 [-7.201, 6.750] 0.949

Produced: 18 December 2020, 5:05

Page 7 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 24.2.12i Statistical Analysis of Percentage of Asthma Control Days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Asthma Control Day					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	11.808	10.846	9.651		
[95% CI]	[8.866, 14.749]	[7.898, 13.794]	[5.500, 13.802]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.962 [-3.203, 5.127] 0.650
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.157 [-2.930, 7.244] 0.405
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.195 [-6.287, 3.897] 0.645
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	15.041	13.023	12.170		
[95% CI]	[11.819, 18.263]	[9.790, 16.257]	[7.617, 16.724]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.018 [-2.548, 6.583] 0.386
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.871 [-2.707, 8.449] 0.313
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.853 [-6.439, 4.732] 0.764

Produced: 18 December 2020, 5:05

Page 8 of 8

Source: Listing 16.2.6.6.3

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

ADDITIONAL_TLF_BATCH2_RESCUE_MEDICATION_USE

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch2

Date of Production: 17/12/2020

Identification Code: Additional_TLF_batch2_Rescue_Medication_use_CCD-05993AB2-02_20201217(Batch2)

Table 16.2.11a Statistical Analysis of Average Use of Rescue Medication including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.533
Inter-Visit Period			0.181
Treatment*Inter-Visit Period			0.049*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.789
Age Group Treatment Interaction			0.838

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11b Statistical Analysis of Average Use of Rescue Medication including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.201
Inter-Visit Period			0.182
Treatment*Inter-Visit Period			0.050*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.185
Gender Treatment Interaction			0.213

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11c Statistical Analysis of Average Use of Rescue Medication including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.272
Inter-Visit Period			0.181
Treatment*Inter-Visit Period			0.050*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.815
BMI Class Treatment Interaction			0.821

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11d Statistical Analysis of Average Use of Rescue Medication including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.042*
Inter-Visit Period			0.182
Treatment*Inter-Visit Period			0.050
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.979
Smoking Status Treatment Interaction			0.057

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11e Statistical Analysis of Average Use of Rescue Medication including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.094
Inter-Visit Period			0.180
Treatment*Inter-Visit Period			0.049*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.247
Number of Exacerbation in the Previous year Treatment Interaction			0.141

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11f Statistical Analysis of Average Use of Rescue Medication including Degree of reversibility at screening (delta FEV1) - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.317
Inter-Visit Period			0.181
Treatment*Inter-Visit Period			0.049*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.215
Degree of reversibility at screening (delta FEV1)			0.983
Treatment Interaction			

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11g Statistical Analysis of Average Use of Rescue Medication including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.584
Inter-Visit Period			0.181
Treatment*Inter-Visit Period			0.049*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.302
Use of Spacer Treatment Interaction			0.523

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11h Statistical Analysis of Average Use of Rescue Medication including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.337
Inter-Visit Period			0.182
Treatment*Inter-Visit Period			0.050*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.621
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.313

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.11i Statistical Analysis of Average Use of Rescue Medication including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Average Rescue Medication Use (puffs/day)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.306
Inter-Visit Period			0.181
Treatment*Inter-Visit Period			0.049*
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.915
Region Treatment Interaction			0.885

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: <65 years old					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.105	
Inter-Visit Period				0.353	
Treatment*Inter-Visit Period				0.377	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.415	-0.390	-0.542		
[95% CI]	[-0.492, -0.337]	[-0.470, -0.310]	[-0.650, -0.434]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.136, 0.086] 0.659
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.127 [-0.005, 0.260] 0.060
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.152 [-0.286, -0.018] 0.026*

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.529	-0.520	-0.657		
[95% CI]	[-0.614, -0.443]	[-0.608, -0.432]	[-0.776, -0.538]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.132, 0.114] 0.885
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.128 [-0.018, 0.275] 0.086
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.137 [-0.285, 0.011] 0.069
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.622	-0.564	-0.732		
[95% CI]	[-0.713, -0.531]	[-0.657, -0.470]	[-0.859, -0.606]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.058 [-0.189, 0.072] 0.380
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.110 [-0.046, 0.266] 0.166
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.168 [-0.326, -0.011] 0.036*

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.683	-0.570	-0.729		
[95% CI]	[-0.776, -0.589]	[-0.667, -0.474]	[-0.859, -0.599]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.112 [-0.247, 0.022] 0.101
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.046 [-0.114, 0.206] 0.573
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.158 [-0.320, 0.004] 0.055
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.704	-0.588	-0.702		
[95% CI]	[-0.801, -0.607]	[-0.688, -0.488]	[-0.837, -0.567]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.116 [-0.255, 0.023] 0.103
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.168, 0.164] 0.980
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.114 [-0.282, 0.054] 0.184

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.562	-0.523	-0.680		
[95% CI]	[-0.642, -0.481]	[-0.606, -0.440]	[-0.792, -0.568]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.154, 0.078] 0.518
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.118 [-0.020, 0.256] 0.093
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.156 [-0.296, -0.017] 0.028*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.627	-0.551	-0.698		
[95% CI]	[-0.710, -0.544]	[-0.637, -0.465]	[-0.814, -0.582]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.076 [-0.196, 0.043] 0.212
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.071 [-0.072, 0.214] 0.328
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.147 [-0.291, -0.003] 0.045*

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.973	
Inter-Visit Period				0.030*	
Treatment*Inter-Visit Period				0.524	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.416	-0.497	-0.569		
[95% CI]	[-0.600, -0.231]	[-0.664, -0.331]	[-0.856, -0.282]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.082 [-0.167, 0.331] 0.518
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.154 [-0.187, 0.494] 0.376
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.072 [-0.406, 0.262] 0.672

Produced: 17 December 2020 Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.640	-0.617	-0.678		
[95% CI]	[-0.811, -0.470]	[-0.771, -0.464]	[-0.944, -0.412]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.023 [-0.253, 0.207] 0.843
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.037 [-0.278, 0.353] 0.816
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.060 [-0.369, 0.249] 0.700
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.700	-0.643	-0.734		
[95% CI]	[-0.889, -0.511]	[-0.814, -0.472]	[-1.030, -0.438]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.312, 0.198] 0.661
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.034 [-0.317, 0.385] 0.849
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.091 [-0.435, 0.253] 0.604

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.683	-0.679	-0.680		
[95% CI]	[-0.888, -0.477]	[-0.865, -0.493]	[-1.004, -0.357]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.281, 0.274] 0.980
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.384, 0.380] 0.991
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.376, 0.373] 0.994
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.817	-0.720	-0.662		
[95% CI]	[-1.030, -0.604]	[-0.914, -0.526]	[-0.999, -0.325]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.097 [-0.385, 0.192] 0.510
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.155 [-0.553, 0.243] 0.444
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.058 [-0.332, 0.449] 0.769

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12a Statistical Analysis of Average Use of Rescue Medication by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.638	-0.613	-0.691		
[95% CI]	[-0.806, -0.469]	[-0.765, -0.461]	[-0.954, -0.428]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.252, 0.202] 0.828
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.053 [-0.259, 0.365] 0.737
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.078 [-0.384, 0.227] 0.613
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.691	-0.655	-0.682		
[95% CI]	[-0.872, -0.510]	[-0.819, -0.492]	[-0.965, -0.398]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.280, 0.208] 0.773
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-0.345, 0.326] 0.955
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.355, 0.303] 0.876

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.327	
Inter-Visit Period				0.459	
Treatment*Inter-Visit Period				0.522	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.328	-0.391	-0.549		
[95% CI]	[-0.458, -0.198]	[-0.512, -0.269]	[-0.736, -0.362]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.063 [-0.116, 0.241] 0.490
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.221 [-0.007, 0.450] 0.058
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.158 [-0.382, 0.065] 0.164

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.483	-0.458	-0.640		
[95% CI]	[-0.625, -0.342]	[-0.590, -0.326]	[-0.843, -0.437]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.219, 0.168] 0.795
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.157 [-0.091, 0.404] 0.215
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.182 [-0.424, 0.060] 0.140
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.548	-0.496	-0.671		
[95% CI]	[-0.695, -0.400]	[-0.634, -0.358]	[-0.883, -0.459]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.052 [-0.254, 0.150] 0.614
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.123 [-0.136, 0.382] 0.351
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.175 [-0.428, 0.078] 0.175

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.603	-0.533	-0.715		
[95% CI]	[-0.752, -0.454]	[-0.672, -0.393]	[-0.930, -0.500]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.070 [-0.275, 0.134] 0.499
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.112 [-0.150, 0.374] 0.401
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.182 [-0.439, 0.074] 0.163
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.687	-0.545	-0.681		
[95% CI]	[-0.840, -0.534]	[-0.688, -0.402]	[-0.901, -0.461]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.142 [-0.351, 0.067] 0.182
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.275, 0.262] 0.962
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.136 [-0.398, 0.127] 0.310

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.494	-0.468	-0.643		
[95% CI]	[-0.627, -0.362]	[-0.592, -0.344]	[-0.833, -0.452]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.026 [-0.208, 0.155] 0.777
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.148 [-0.084, 0.381] 0.211
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.175 [-0.402, 0.053] 0.132
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.568	-0.503	-0.671		
[95% CI]	[-0.702, -0.434]	[-0.629, -0.378]	[-0.864, -0.478]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.065 [-0.248, 0.119] 0.489
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.103 [-0.133, 0.338] 0.391
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.168 [-0.398, 0.063] 0.153

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.776	
Inter-Visit Period				0.200	
Treatment*Inter-Visit Period				0.206	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.467	-0.435	-0.534		
[95% CI]	[-0.551, -0.383]	[-0.523, -0.347]	[-0.651, -0.417]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.154, 0.089] 0.600
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.067 [-0.077, 0.211] 0.360
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.100 [-0.246, 0.047] 0.182

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.587	-0.617	-0.645		
[95% CI]	[-0.676, -0.499]	[-0.710, -0.524]	[-0.769, -0.521]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.030 [-0.099, 0.158] 0.650
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.058 [-0.095, 0.210] 0.460
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.183, 0.127] 0.725
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.688	-0.660	-0.741		
[95% CI]	[-0.785, -0.591]	[-0.762, -0.558]	[-0.877, -0.605]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.028 [-0.169, 0.113] 0.696
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.053 [-0.114, 0.220] 0.534
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.081 [-0.251, 0.089] 0.349

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.728	-0.656	-0.703		
[95% CI]	[-0.832, -0.625]	[-0.764, -0.548]	[-0.847, -0.558]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.222, 0.077] 0.341
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.204, 0.152] 0.775
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.227, 0.134] 0.612
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.742	-0.685	-0.683		
[95% CI]	[-0.850, -0.634]	[-0.799, -0.571]	[-0.835, -0.531]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.057 [-0.214, 0.100] 0.478
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.059 [-0.246, 0.128] 0.535
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.188, 0.192] 0.981

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12b Statistical Analysis of Average Use of Rescue Medication by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.623	-0.612	-0.680		
[95% CI]	[-0.708, -0.538]	[-0.701, -0.523]	[-0.798, -0.561]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.134, 0.112] 0.862
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.057 [-0.089, 0.203] 0.447
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.067 [-0.216, 0.081] 0.372
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.679	-0.641	-0.686		
[95% CI]	[-0.770, -0.588]	[-0.736, -0.546]	[-0.814, -0.559]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.038 [-0.170, 0.093] 0.569
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.149, 0.164] 0.924
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.046 [-0.204, 0.113] 0.572

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: < 25					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.146	
Inter-Visit Period				0.539	
Treatment*Inter-Visit Period				0.616	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.337	-0.352	-0.518		
[95% CI]	[-0.478, -0.195]	[-0.488, -0.216]	[-0.721, -0.315]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.016 [-0.181, 0.212] 0.876
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.182 [-0.066, 0.429] 0.150
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.166 [-0.410, 0.078] 0.182

Produced: 17 December 2020

Page 1 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.482	-0.436	-0.661		
[95% CI]	[-0.621, -0.343]	[-0.569, -0.303]	[-0.860, -0.462]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.238, 0.147] 0.643
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.179 [-0.063, 0.422] 0.147
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.225 [-0.464, 0.014] 0.065
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.581	-0.509	-0.762		
[95% CI]	[-0.726, -0.436]	[-0.647, -0.370]	[-0.969, -0.555]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.072 [-0.273, 0.128] 0.478
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.181 [-0.072, 0.434] 0.161
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.253 [-0.502, -0.004] 0.046*

Produced: 17 December 2020

Page 2 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.632	-0.500	-0.738		
[95% CI]	[-0.791, -0.474]	[-0.652, -0.349]	[-0.965, -0.510]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.132 [-0.351, 0.087] 0.237
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.105 [-0.172, 0.382] 0.456
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.237 [-0.510, 0.036] 0.088
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.701	-0.502	-0.735		
[95% CI]	[-0.864, -0.537]	[-0.657, -0.347]	[-0.969, -0.501]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.199 [-0.424, 0.027] 0.084
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [-0.251, 0.320] 0.812
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.233 [-0.514, 0.048] 0.104

Produced: 17 December 2020

Page 3 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.513	-0.462	-0.693		
[95% CI]	[-0.642, -0.384]	[-0.586, -0.339]	[-0.878, -0.509]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.051 [-0.229, 0.128] 0.578
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.180 [-0.045, 0.406] 0.116
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.231 [-0.453, -0.009] 0.042*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.588	-0.482	-0.715		
[95% CI]	[-0.726, -0.451]	[-0.613, -0.350]	[-0.911, -0.518]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.107 [-0.297, 0.083] 0.271
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.127 [-0.113, 0.366] 0.300
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.233 [-0.469, 0.003] 0.053

Produced: 17 December 2020

Page 4 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: [25-30)					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.787	
Inter-Visit Period				0.228	
Treatment*Inter-Visit Period				0.965	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.452	-0.483	-0.537		
[95% CI]	[-0.558, -0.346]	[-0.593, -0.374]	[-0.685, -0.390]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.032 [-0.121, 0.184] 0.683
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.085 [-0.096, 0.267] 0.356
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.238, 0.130] 0.567

Produced: 17 December 2020

Page 5 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.542	-0.600	-0.635		
[95% CI]	[-0.672, -0.412]	[-0.734, -0.466]	[-0.817, -0.453]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.058 [-0.129, 0.245] 0.542
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.093 [-0.130, 0.316] 0.413
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.261, 0.191] 0.760
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.621	-0.665	-0.716		
[95% CI]	[-0.752, -0.489]	[-0.802, -0.528]	[-0.901, -0.531]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.044 [-0.145, 0.234] 0.646
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.096 [-0.132, 0.323] 0.409
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.051 [-0.281, 0.179] 0.663

Produced: 17 December 2020

Page 6 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.653	-0.693	-0.695		
[95% CI]	[-0.785, -0.522]	[-0.830, -0.556]	[-0.881, -0.509]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.040 [-0.150, 0.229] 0.681
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.042 [-0.186, 0.269] 0.718
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.233, 0.228] 0.985
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.693	-0.696	-0.711		
[95% CI]	[-0.828, -0.558]	[-0.836, -0.556]	[-0.902, -0.520]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.191, 0.198] 0.975
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.215, 0.252] 0.877
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.252, 0.222] 0.899

Produced: 17 December 2020

Page 7 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.570	-0.617	-0.664		
[95% CI]	[-0.689, -0.452]	[-0.740, -0.494]	[-0.830, -0.497]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.047 [-0.124, 0.217] 0.592
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.093 [-0.111, 0.297] 0.370
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.253, 0.160] 0.658
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.621	-0.656	-0.683		
[95% CI]	[-0.741, -0.501]	[-0.780, -0.531]	[-0.852, -0.514]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.035 [-0.138, 0.208] 0.694
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.062 [-0.145, 0.269] 0.556
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.237, 0.183] 0.798

Produced: 17 December 2020

Page 8 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: >=30					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.571	
Inter-Visit Period				0.337	
Treatment*Inter-Visit Period				0.247	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.430	-0.399	-0.569		
[95% CI]	[-0.559, -0.300]	[-0.529, -0.269]	[-0.752, -0.386]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.215, 0.153] 0.743
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.139 [-0.085, 0.364] 0.224
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.170 [-0.395, 0.055] 0.138

Produced: 17 December 2020

Page 9 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.604	-0.584	-0.660		
[95% CI]	[-0.734, -0.475]	[-0.714, -0.454]	[-0.843, -0.477]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.204, 0.164] 0.829
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.055 [-0.169, 0.280] 0.627
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.076 [-0.300, 0.149] 0.508
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.693	-0.577	-0.703		
[95% CI]	[-0.841, -0.544]	[-0.726, -0.429]	[-0.911, -0.494]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.116 [-0.326, 0.095] 0.281
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.246, 0.266] 0.940
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.125 [-0.381, 0.131] 0.337

Produced: 17 December 2020 Page 10 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.751	-0.596	-0.709		
[95% CI]	[-0.906, -0.595]	[-0.752, -0.441]	[-0.927, -0.491]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.154 [-0.374, 0.066] 0.169
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.041 [-0.309, 0.226] 0.761
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.113 [-0.381, 0.155] 0.409
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.771	-0.652	-0.627		
[95% CI]	[-0.935, -0.607]	[-0.816, -0.488]	[-0.857, -0.397]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.119 [-0.352, 0.113] 0.313
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.144 [-0.427, 0.138] 0.316
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.257, 0.308] 0.861

Produced: 17 December 2020 Page 11 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12c Statistical Analysis of Average Use of Rescue Medication by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.625	-0.552	-0.669		
[95% CI]	[-0.754, -0.496]	[-0.681, -0.423]	[-0.851, -0.487]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.256, 0.110] 0.432
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.044 [-0.179, 0.267] 0.700
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.117 [-0.340, 0.106] 0.304
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.693	-0.587	-0.670		
[95% CI]	[-0.829, -0.556]	[-0.724, -0.450]	[-0.862, -0.478]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.106 [-0.299, 0.088] 0.284
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.258, 0.213] 0.851
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.083 [-0.319, 0.153] 0.490

Produced: 17 December 2020 Page 12 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.625	
Inter-Visit Period				0.249	
Treatment*Inter-Visit Period				0.204	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.423	-0.452	-0.490		
[95% CI]	[-0.500, -0.346]	[-0.528, -0.375]	[-0.599, -0.382]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.029 [-0.080, 0.137] 0.604
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.068 [-0.065, 0.200] 0.317
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.171, 0.094] 0.565

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.568	-0.587	-0.623		
[95% CI]	[-0.646, -0.489]	[-0.666, -0.509]	[-0.735, -0.512]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.020 [-0.092, 0.131] 0.727
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.056 [-0.081, 0.192] 0.424
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.172, 0.101] 0.607
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.664	-0.622	-0.737		
[95% CI]	[-0.749, -0.580]	[-0.707, -0.538]	[-0.857, -0.618]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.161, 0.077] 0.490
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.073 [-0.073, 0.219] 0.326
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.115 [-0.261, 0.031] 0.122

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.703	-0.640	-0.721		
[95% CI]	[-0.792, -0.614]	[-0.730, -0.551]	[-0.847, -0.594]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.063 [-0.189, 0.064] 0.331
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.137, 0.173] 0.822
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.080 [-0.235, 0.074] 0.309
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.750	-0.662	-0.705		
[95% CI]	[-0.843, -0.657]	[-0.755, -0.569]	[-0.837, -0.573]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.088 [-0.220, 0.043] 0.189
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.045 [-0.206, 0.117] 0.588
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-0.205, 0.118] 0.597

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.597	-0.585	-0.664		
[95% CI]	[-0.672, -0.522]	[-0.660, -0.510]	[-0.770, -0.558]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.118, 0.094] 0.822
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.067 [-0.063, 0.197] 0.312
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.079 [-0.209, 0.051] 0.232
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.661	-0.618	-0.689		
[95% CI]	[-0.740, -0.582]	[-0.696, -0.539]	[-0.800, -0.578]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.043 [-0.155, 0.068] 0.446
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.028 [-0.109, 0.164] 0.688
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.071 [-0.208, 0.065] 0.306

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.074	
Inter-Visit Period				0.331	
Treatment*Inter-Visit Period				0.619	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.354	-0.184	-0.884		
[95% CI]	[-0.550, -0.158]	[-0.385, 0.016]	[-1.161, -0.607]		
p-value	<0.001***	0.072	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.169 [-0.450, 0.111] 0.235
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.531 [0.190, 0.871] 0.002**
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.700 [-1.042, -0.358] <0.001***

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.414	-0.302	-0.854		
[95% CI]	[-0.662, -0.165]	[-0.556, -0.047]	[-1.205, -0.503]		
p-value	0.001**	0.020*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.112 [-0.467, 0.243] 0.535
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.440 [0.009, 0.871] 0.046*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.552 [-0.986, -0.118] 0.013*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.437	-0.372	-0.717		
[95% CI]	[-0.697, -0.176]	[-0.637, -0.106]	[-1.085, -0.350]		
p-value	0.001**	0.006**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.065 [-0.436, 0.306] 0.730
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.281 [-0.171, 0.732] 0.221
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.346 [-0.800, 0.108] 0.134

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.537	-0.364	-0.712		
[95% CI]	[-0.793, -0.281]	[-0.626, -0.102]	[-1.077, -0.346]		
p-value	<0.001***	0.007**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.173 [-0.539, 0.193] 0.351
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.175 [-0.273, 0.622] 0.443
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.348 [-0.798, 0.103] 0.129
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.534	-0.382	-0.644		
[95% CI]	[-0.793, -0.275]	[-0.646, -0.118]	[-1.013, -0.276]		
p-value	<0.001***	0.005**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.152 [-0.521, 0.217] 0.417
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.110 [-0.341, 0.562] 0.630
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.263 [-0.716, 0.191] 0.255

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12d Statistical Analysis of Average Use of Rescue Medication by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.417	-0.321	-0.785		
[95% CI]	[-0.647, -0.187]	[-0.556, -0.086]	[-1.110, -0.460]		
p-value	<0.001***	0.008**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.096 [-0.424, 0.233] 0.567
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.368 [-0.031, 0.767] 0.070
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.464 [-0.865, -0.063] 0.024*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.476	-0.347	-0.733		
[95% CI]	[-0.707, -0.245]	[-0.583, -0.111]	[-1.060, -0.406]		
p-value	<0.001***	0.004**	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.130 [-0.460, 0.201] 0.440
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.257 [-0.145, 0.658] 0.209
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.386 [-0.790, 0.018] 0.061

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	439	451	229		
Effect					
Treatment				0.762	
Inter-Visit Period				0.199	
Treatment*Inter-Visit Period				0.148	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.393	-0.419	-0.480		
[95% CI]	[-0.473, -0.313]	[-0.498, -0.340]	[-0.590, -0.369]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.026 [-0.086, 0.139] 0.644
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.087 [-0.049, 0.224] 0.211
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.061 [-0.197, 0.075] 0.382

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.521	-0.516	-0.560		
[95% CI]	[-0.607, -0.434]	[-0.601, -0.430]	[-0.680, -0.441]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.127, 0.117] 0.935
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.040 [-0.108, 0.187] 0.599
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.045 [-0.192, 0.103] 0.551
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.606	-0.570	-0.654		
[95% CI]	[-0.697, -0.516]	[-0.660, -0.480]	[-0.780, -0.528]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.165, 0.091] 0.571
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.108, 0.202] 0.552
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.084 [-0.239, 0.071] 0.287

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.651	-0.581	-0.640		
[95% CI]	[-0.746, -0.556]	[-0.675, -0.488]	[-0.772, -0.509]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.070 [-0.203, 0.064] 0.306
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.173, 0.151] 0.896
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.059 [-0.220, 0.103] 0.476
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.681	-0.609	-0.595		
[95% CI]	[-0.779, -0.583]	[-0.706, -0.512]	[-0.732, -0.459]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.210, 0.065] 0.301
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.086 [-0.254, 0.082] 0.316
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.013 [-0.154, 0.180] 0.877

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.547	-0.530	-0.598		
[95% CI]	[-0.629, -0.466]	[-0.610, -0.449]	[-0.711, -0.485]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.132, 0.097] 0.766
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.051 [-0.088, 0.190] 0.472
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.068 [-0.207, 0.070] 0.333
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.606	-0.562	-0.609		
[95% CI]	[-0.691, -0.521]	[-0.646, -0.478]	[-0.726, -0.491]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.163, 0.075] 0.468
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.142, 0.148] 0.970
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.191, 0.097] 0.524

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.080	
Inter-Visit Period				0.335	
Treatment*Inter-Visit Period				0.674	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.492	-0.399	-0.785		
[95% CI]	[-0.653, -0.330]	[-0.568, -0.230]	[-1.028, -0.542]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.092 [-0.326, 0.141] 0.437
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.294 [0.002, 0.586] 0.049*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.386 [-0.682, -0.090] 0.011*

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.641	-0.667	-0.989		
[95% CI]	[-0.810, -0.472]	[-0.843, -0.491]	[-1.245, -0.734]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.026 [-0.218, 0.270] 0.836
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.348 [0.042, 0.655] 0.026*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.323 [-0.633, -0.012] 0.042*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.730	-0.658	-0.985		
[95% CI]	[-0.920, -0.539]	[-0.857, -0.459]	[-1.274, -0.697]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.071 [-0.347, 0.204] 0.610
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.256 [-0.090, 0.602] 0.147
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.327 [-0.678, 0.023] 0.067

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.791	-0.680	-0.975		
[95% CI]	[-0.988, -0.594]	[-0.886, -0.473]	[-1.273, -0.677]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.111 [-0.397, 0.175] 0.444
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.184 [-0.174, 0.541] 0.313
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.295 [-0.657, 0.067] 0.110
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.865	-0.680	-1.024		
[95% CI]	[-1.072, -0.658]	[-0.896, -0.464]	[-1.336, -0.711]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.185 [-0.485, 0.114] 0.224
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.158 [-0.217, 0.534] 0.407
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.344 [-0.724, 0.036] 0.076

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12e Statistical Analysis of Average Use of Rescue Medication by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.666	-0.621	-0.956		
[95% CI]	[-0.830, -0.501]	[-0.793, -0.449]	[-1.205, -0.707]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.283, 0.193] 0.711
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.290 [-0.008, 0.588] 0.057
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.335 [-0.637, -0.033] 0.030*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.745	-0.650	-0.977		
[95% CI]	[-0.917, -0.574]	[-0.829, -0.471]	[-1.236, -0.717]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.095 [-0.343, 0.153] 0.451
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.231 [-0.080, 0.542] 0.145
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.326 [-0.641, -0.011] 0.042*

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.439	
Inter-Visit Period				0.229	
Treatment*Inter-Visit Period				0.292	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.385	-0.384	-0.540		
[95% CI]	[-0.487, -0.283]	[-0.490, -0.279]	[-0.685, -0.395]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.148, 0.145] 0.987
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.154 [-0.023, 0.332] 0.087
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.156 [-0.335, 0.024] 0.089

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.535	-0.553	-0.648		
[95% CI]	[-0.641, -0.430]	[-0.663, -0.444]	[-0.799, -0.498]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.018 [-0.134, 0.170] 0.816
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.113 [-0.071, 0.297] 0.228
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.095 [-0.281, 0.091] 0.317
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.646	-0.578	-0.697		
[95% CI]	[-0.762, -0.531]	[-0.698, -0.458]	[-0.863, -0.532]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.068 [-0.234, 0.099] 0.424
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.051 [-0.151, 0.253] 0.618
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.119 [-0.323, 0.085] 0.253

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.689	-0.555	-0.665		
[95% CI]	[-0.814, -0.565]	[-0.684, -0.425]	[-0.844, -0.487]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.135 [-0.314, 0.045] 0.141
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.242, 0.194] 0.830
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.111 [-0.331, 0.110] 0.324
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.706	-0.556	-0.625		
[95% CI]	[-0.835, -0.578]	[-0.690, -0.423]	[-0.811, -0.440]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.150 [-0.336, 0.036] 0.113
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.081 [-0.307, 0.145] 0.481
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.069 [-0.298, 0.160] 0.553

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.572	-0.541	-0.658		
[95% CI]	[-0.673, -0.471]	[-0.646, -0.436]	[-0.802, -0.514]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.177, 0.114] 0.675
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.086 [-0.090, 0.262] 0.338
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.117 [-0.296, 0.061] 0.198
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.635	-0.548	-0.652		
[95% CI]	[-0.743, -0.527]	[-0.660, -0.436]	[-0.807, -0.498]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.242, 0.069] 0.276
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.171, 0.207] 0.852
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.104 [-0.295, 0.087] 0.284

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.482	
Inter-Visit Period				0.039*	
Treatment*Inter-Visit Period				0.767	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.441	-0.449	-0.549		
[95% CI]	[-0.542, -0.341]	[-0.546, -0.351]	[-0.689, -0.409]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.133, 0.147] 0.919
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.107 [-0.065, 0.280] 0.223
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.100 [-0.270, 0.071] 0.250

Produced: 17 December 2020 Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.554	-0.546	-0.653		
[95% CI]	[-0.668, -0.441]	[-0.655, -0.436]	[-0.811, -0.495]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.009 [-0.167, 0.149] 0.914
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.098 [-0.096, 0.293] 0.322
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.107 [-0.299, 0.085] 0.276
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.619	-0.599	-0.746		
[95% CI]	[-0.738, -0.500]	[-0.713, -0.484]	[-0.911, -0.581]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.020 [-0.186, 0.145] 0.808
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.127 [-0.076, 0.331] 0.220
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.148 [-0.349, 0.053] 0.150

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.668	-0.650	-0.760		
[95% CI]	[-0.785, -0.552]	[-0.763, -0.537]	[-0.923, -0.597]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.181, 0.144] 0.827
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.091 [-0.109, 0.292] 0.371
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.109 [-0.308, 0.089] 0.279
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.736	-0.692	-0.748		
[95% CI]	[-0.857, -0.614]	[-0.809, -0.575]	[-0.917, -0.579]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.043 [-0.212, 0.125] 0.614
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.012 [-0.195, 0.220] 0.907
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.261, 0.150] 0.595

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12f Statistical Analysis of Average Use of Rescue Medication by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.572	-0.559	-0.687		
[95% CI]	[-0.678, -0.465]	[-0.662, -0.456]	[-0.835, -0.539]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.013 [-0.161, 0.136] 0.868
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.115 [-0.068, 0.298] 0.216
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.128 [-0.308, 0.053] 0.165
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.636	-0.614	-0.721		
[95% CI]	[-0.743, -0.528]	[-0.718, -0.511]	[-0.870, -0.571]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.021 [-0.170, 0.128] 0.781
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.085 [-0.099, 0.269] 0.364
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.106 [-0.288, 0.076] 0.252

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.400	
Inter-Visit Period				0.202	
Treatment*Inter-Visit Period				0.432	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.556	-0.451	-0.609		
[95% CI]	[-0.713, -0.400]	[-0.602, -0.299]	[-0.815, -0.402]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.106 [-0.324, 0.113] 0.342
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.052 [-0.207, 0.312] 0.691
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.158 [-0.414, 0.098] 0.226

Produced: 17 December 2020 Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.649	-0.563	-0.733		
[95% CI]	[-0.815, -0.482]	[-0.725, -0.401]	[-0.953, -0.512]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.318, 0.146] 0.467
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.084 [-0.192, 0.360] 0.551
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.170 [-0.443, 0.103] 0.223
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.657	-0.578	-0.741		
[95% CI]	[-0.838, -0.477]	[-0.753, -0.403]	[-0.979, -0.503]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.079 [-0.331, 0.172] 0.535
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.084 [-0.215, 0.382] 0.581
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.163 [-0.458, 0.132] 0.278

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.811	-0.614	-0.706		
[95% CI]	[-0.990, -0.632]	[-0.788, -0.440]	[-0.942, -0.470]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.197 [-0.447, 0.052] 0.121
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.105 [-0.401, 0.191] 0.487
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.092 [-0.385, 0.201] 0.536
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.806	-0.645	-0.807		
[95% CI]	[-1.002, -0.610]	[-0.835, -0.454]	[-1.066, -0.548]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.161 [-0.435, 0.112] 0.246
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.324, 0.325] 0.998
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.162 [-0.483, 0.159] 0.322

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.639	-0.554	-0.718		
[95% CI]	[-0.800, -0.478]	[-0.710, -0.398]	[-0.931, -0.506]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.085 [-0.310, 0.139] 0.455
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.079 [-0.188, 0.346] 0.560
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.164 [-0.428, 0.099] 0.221
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.724	-0.591	-0.735		
[95% CI]	[-0.889, -0.559]	[-0.751, -0.431]	[-0.953, -0.518]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.133 [-0.363, 0.097] 0.255
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.262, 0.284] 0.935
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.144 [-0.414, 0.126] 0.294

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.442	
Inter-Visit Period				0.516	
Treatment*Inter-Visit Period				0.052	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.372	-0.404	-0.521		
[95% CI]	[-0.453, -0.291]	[-0.486, -0.323]	[-0.637, -0.405]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.032 [-0.083, 0.147] 0.583
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.149 [0.007, 0.290] 0.039*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.117 [-0.258, 0.025] 0.107

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.515	-0.544	-0.622		
[95% CI]	[-0.602, -0.428]	[-0.632, -0.457]	[-0.747, -0.497]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.029 [-0.094, 0.153] 0.640
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.107 [-0.045, 0.259] 0.168
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.078 [-0.230, 0.075] 0.319
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.628	-0.592	-0.714		
[95% CI]	[-0.720, -0.536]	[-0.685, -0.499]	[-0.848, -0.581]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.036 [-0.167, 0.095] 0.591
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.087 [-0.075, 0.248] 0.294
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.122 [-0.285, 0.040] 0.140

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.641	-0.599	-0.713		
[95% CI]	[-0.738, -0.544]	[-0.698, -0.501]	[-0.854, -0.572]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.180, 0.097] 0.555
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.072 [-0.099, 0.244] 0.409
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.114 [-0.286, 0.058] 0.194
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.694	-0.619	-0.643		
[95% CI]	[-0.793, -0.594]	[-0.719, -0.518]	[-0.787, -0.500]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.075 [-0.216, 0.066] 0.299
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.050 [-0.225, 0.125] 0.573
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.200, 0.151] 0.783

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12g Statistical Analysis of Average Use of Rescue Medication by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.554	-0.548	-0.656		
[95% CI]	[-0.635, -0.472]	[-0.631, -0.466]	[-0.774, -0.539]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.121, 0.111] 0.928
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.102 [-0.041, 0.246] 0.161
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.108 [-0.252, 0.036] 0.142
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.610	-0.578	-0.669		
[95% CI]	[-0.695, -0.524]	[-0.665, -0.492]	[-0.792, -0.545]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.031 [-0.153, 0.091] 0.615
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.059 [-0.091, 0.209] 0.441
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.090 [-0.241, 0.061] 0.241

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.338	
Inter-Visit Period				0.063	
Treatment*Inter-Visit Period				0.098	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.464	-0.439	-0.586		
[95% CI]	[-0.574, -0.354]	[-0.546, -0.331]	[-0.743, -0.429]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.179, 0.129] 0.752
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.122 [-0.069, 0.314] 0.211
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.147 [-0.337, 0.043] 0.130

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.625	-0.546	-0.658		
[95% CI]	[-0.739, -0.511]	[-0.658, -0.434]	[-0.821, -0.495]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.079 [-0.239, 0.081] 0.330
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.033 [-0.166, 0.231] 0.748
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.112 [-0.309, 0.086] 0.267
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.733	-0.588	-0.697		
[95% CI]	[-0.857, -0.609]	[-0.709, -0.467]	[-0.874, -0.521]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.145 [-0.318, 0.028] 0.101
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.035 [-0.251, 0.180] 0.747
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.110 [-0.324, 0.105] 0.316

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.781	-0.624	-0.640		
[95% CI]	[-0.911, -0.651]	[-0.752, -0.496]	[-0.825, -0.454]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.157 [-0.340, 0.025] 0.091
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.141 [-0.368, 0.085] 0.221
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.241, 0.210] 0.891
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.821	-0.657	-0.595		
[95% CI]	[-0.956, -0.686]	[-0.789, -0.525]	[-0.787, -0.403]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.164 [-0.353, 0.025] 0.088
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.226 [-0.461, 0.009] 0.059
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.062 [-0.172, 0.295] 0.604

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.658	-0.552	-0.668		
[95% CI]	[-0.768, -0.548]	[-0.660, -0.444]	[-0.825, -0.511]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.106 [-0.260, 0.048] 0.176
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.182, 0.201] 0.921
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.116 [-0.306, 0.074] 0.232
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.729	-0.596	-0.644		
[95% CI]	[-0.844, -0.614]	[-0.708, -0.483]	[-0.808, -0.479]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.133 [-0.295, 0.028] 0.105
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.085 [-0.286, 0.115] 0.403
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.048 [-0.247, 0.151] 0.636

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.121	
Inter-Visit Period				0.382	
Treatment*Inter-Visit Period				0.644	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.368	-0.393	-0.503		
[95% CI]	[-0.462, -0.274]	[-0.489, -0.297]	[-0.633, -0.372]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.025 [-0.109, 0.159] 0.713
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.135 [-0.026, 0.295] 0.100
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.109 [-0.272, 0.053] 0.186

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.472	-0.554	-0.640		
[95% CI]	[-0.576, -0.368]	[-0.661, -0.448]	[-0.786, -0.495]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.082 [-0.067, 0.231] 0.280
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.168 [-0.011, 0.347] 0.065
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.086 [-0.267, 0.095] 0.350
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.542	-0.591	-0.741		
[95% CI]	[-0.651, -0.433]	[-0.703, -0.479]	[-0.894, -0.588]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.049 [-0.107, 0.206] 0.537
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.199 [0.011, 0.387] 0.038*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.150 [-0.340, 0.040] 0.123

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.587	-0.584	-0.773		
[95% CI]	[-0.699, -0.475]	[-0.698, -0.469]	[-0.930, -0.615]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.163, 0.157] 0.968
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.186 [-0.008, 0.379] 0.060
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.189 [-0.384, 0.006] 0.058
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.630	-0.594	-0.766		
[95% CI]	[-0.746, -0.513]	[-0.713, -0.475]	[-0.930, -0.602]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-0.202, 0.131] 0.677
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.136 [-0.065, 0.337] 0.185
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.171 [-0.374, 0.031] 0.098

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12h Statistical Analysis of Average Use of Rescue Medication by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.494	-0.549	-0.673		
[95% CI]	[-0.591, -0.397]	[-0.649, -0.450]	[-0.809, -0.538]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.056 [-0.083, 0.194] 0.431
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.180 [0.013, 0.346] 0.035*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.124 [-0.292, 0.044] 0.148
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.550	-0.569	-0.721		
[95% CI]	[-0.650, -0.450]	[-0.672, -0.467]	[-0.862, -0.581]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.124, 0.162] 0.797
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.171 [-0.001, 0.343] 0.052
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.152 [-0.326, 0.022] 0.086

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.774	
Inter-Visit Period				0.072	
Treatment*Inter-Visit Period				0.653	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.319	-0.385	-0.425		
[95% CI]	[-0.406, -0.233]	[-0.472, -0.299]	[-0.546, -0.303]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.066 [-0.056, 0.188] 0.289
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.105 [-0.044, 0.255] 0.166
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.189, 0.110] 0.604

Produced: 17 December 2020

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.425	-0.477	-0.490		
[95% CI]	[-0.517, -0.332]	[-0.570, -0.384]	[-0.621, -0.358]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.052 [-0.079, 0.184] 0.436
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.065 [-0.096, 0.226] 0.428
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.174, 0.148] 0.876
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.475	-0.505	-0.537		
[95% CI]	[-0.574, -0.376]	[-0.604, -0.405]	[-0.677, -0.397]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.030 [-0.110, 0.170] 0.676
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.062 [-0.109, 0.234] 0.474
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.204, 0.139] 0.708

Produced: 17 December 2020

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.507	-0.516	-0.554		
[95% CI]	[-0.606, -0.408]	[-0.615, -0.416]	[-0.695, -0.414]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.132, 0.149] 0.905
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.125, 0.219] 0.590
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.211, 0.133] 0.659
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.563	-0.532	-0.549		
[95% CI]	[-0.660, -0.466]	[-0.629, -0.434]	[-0.687, -0.412]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.032 [-0.169, 0.106] 0.652
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.014 [-0.182, 0.154] 0.872
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.186, 0.151] 0.836

Produced: 17 December 2020

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.435	-0.478	-0.505		
[95% CI]	[-0.525, -0.346]	[-0.568, -0.388]	[-0.632, -0.379]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.042 [-0.085, 0.169] 0.513
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.070 [-0.085, 0.225] 0.376
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.183, 0.128] 0.727
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.484	-0.500	-0.529		
[95% CI]	[-0.574, -0.395]	[-0.590, -0.411]	[-0.655, -0.402]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.016 [-0.111, 0.143] 0.803
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.044 [-0.111, 0.199] 0.574
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.183, 0.127] 0.720

Produced: 17 December 2020

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
Average Rescue Medication Use (puffs/day)					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.111	
Inter-Visit Period				0.211	
Treatment*Inter-Visit Period				0.328	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	-0.537	-0.449	-0.689		
[95% CI]	[-0.656, -0.417]	[-0.569, -0.330]	[-0.858, -0.521]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.087 [-0.257, 0.082] 0.312
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.152 [-0.054, 0.359] 0.148
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.240 [-0.446, -0.033] 0.023*

Produced: 17 December 2020

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	-0.699	-0.637	-0.850		
[95% CI]	[-0.828, -0.570]	[-0.766, -0.508]	[-1.031, -0.668]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.062 [-0.245, 0.120] 0.502
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.150 [-0.073, 0.373] 0.186
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.213 [-0.436, 0.010] 0.062
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	-0.832	-0.693	-0.952		
[95% CI]	[-0.970, -0.693]	[-0.833, -0.554]	[-1.148, -0.756]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.139 [-0.335, 0.058] 0.167
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.121 [-0.120, 0.361] 0.325
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.259 [-0.500, -0.018] 0.035*

Produced: 17 December 2020

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	-0.900	-0.707	-0.905		
[95% CI]	[-1.047, -0.752]	[-0.856, -0.559]	[-1.114, -0.696]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.192 [-0.402, 0.017] 0.071
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.251, 0.261] 0.969
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.198 [-0.454, 0.058] 0.130
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	-0.930	-0.736	-0.851		
[95% CI]	[-1.088, -0.773]	[-0.895, -0.578]	[-1.074, -0.627]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.194 [-0.418, 0.030] 0.089
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.080 [-0.353, 0.194] 0.567
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.114 [-0.388, 0.160] 0.413

Produced: 17 December 2020

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 16.2.12i Statistical Analysis of Average Use of Rescue Medication by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Average Rescue Medication Use (puffs/day)					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	-0.746	-0.638	-0.880		
[95% CI]	[-0.866, -0.625]	[-0.759, -0.517]	[-1.050, -0.710]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.107 [-0.278, 0.064] 0.218
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.135 [-0.074, 0.343] 0.206
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.242 [-0.451, -0.033] 0.023*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	-0.830	-0.680	-0.880		
[95% CI]	[-0.959, -0.700]	[-0.809, -0.550]	[-1.063, -0.697]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.150 [-0.334, 0.033] 0.108
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.050 [-0.174, 0.274] 0.660
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.200 [-0.425, 0.024] 0.080

Produced: 17 December 2020

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

ADDITIONAL_TLF_BATCH3_RESCUE_MEDICATION_FREE_DAYS

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch3

Date of Production: 18/12/2020

Identification Code: Additional_TLF_batch3_Rescue_Medication_Free_Days_CCD-05993AB2-02_20201218(Batch3)

Table 22.2.11a Statistical Analysis of Percentage of Rescue Medication-free days including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.070
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.843
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Age Group			0.367
Age Group Treatment Interaction			0.236

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11b Statistical Analysis of Percentage of Rescue Medication-free days including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.120
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.842
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Gender			0.054
Gender Treatment Interaction			0.300

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11c Statistical Analysis of Percentage of Rescue Medication-free days including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.133
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.842
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
BMI Class			0.150
BMI Class Treatment Interaction			0.637

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11d Statistical Analysis of Percentage of Rescue Medication-free days including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.093
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.842
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Smoking Status			0.604
Smoking Status Treatment Interaction			0.318

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11e Statistical Analysis of Percentage of Rescue Medication-free days including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.042*
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.843
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.974
Number of Exacerbation in the Previous year Treatment Interaction			0.092

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11f Statistical Analysis of Percentage of Rescue Medication-free days including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.185
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.843
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.509
Degree of reversibility at screening (delta FEV1)			0.285
Treatment Interaction			

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11g Statistical Analysis of Percentage of Rescue Medication-free days including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.207
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.841
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Use of Spacer			0.235
Use of Spacer Treatment Interaction			0.845

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11h Statistical Analysis of Percentage of Rescue Medication-free days including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.184
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.843
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.347
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.610

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.11i Statistical Analysis of Percentage of Rescue Medication-free days including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Percentage of Days without Intake of Rescue Medication			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.161
Inter-Visit Period			<0.001***
Treatment*Inter-Visit Period			0.841
Baseline			<0.001***
Baseline*Inter-Visit Period			<0.001***
Region			0.125
Region Treatment Interaction			0.568

Produced: 18 December 2020, 3:56

Page 1 of 1

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: <65 years old					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.044*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.480	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	10.573	10.335	13.129		
[95% CI]	[8.489, 12.658]	[8.189, 12.481]	[10.239, 16.019]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.239 [-2.753, 3.230] 0.876
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.555 [-6.119, 1.009] 0.160
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.794 [-0.806, 6.393] 0.128

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.787	13.506	16.569		
[95% CI]	[12.355, 17.219]	[11.002, 16.010]	[13.191, 19.947]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.281 [-2.210, 4.771] 0.472
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.782 [-5.946, 2.381] 0.401
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.063 [-1.142, 7.268] 0.153
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.910	14.445	19.734		
[95% CI]	[15.276, 20.544]	[11.737, 17.154]	[16.079, 23.389]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.465 [-0.313, 7.242] 0.072
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.824 [-6.330, 2.682] 0.427
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.289 [0.739, 9.838] 0.023*

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.840	14.551	20.981		
[95% CI]	[16.030, 21.651]	[11.661, 17.442]	[17.075, 24.886]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.289 [0.257, 8.321] 0.037*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.141 [-6.953, 2.672] 0.383
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.430 [1.571, 11.289] 0.010**
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.206	14.762	21.288		
[95% CI]	[16.337, 22.075]	[11.816, 17.708]	[17.300, 25.276]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.444 [0.331, 8.556] 0.034*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.082 [-6.996, 2.831] 0.406
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.526 [1.567, 11.485] 0.010**

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.820	13.524	17.744		
[95% CI]	[13.509, 18.132]	[11.145, 15.903]	[14.536, 20.952]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.296 [-1.020, 5.613] 0.175
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.924 [-5.879, 2.031] 0.340
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.220 [0.226, 8.214] 0.038*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.415	14.086	19.433		
[95% CI]	[14.973, 19.857]	[11.574, 16.598]	[16.043, 22.824]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.328 [-0.175, 6.831] 0.063
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.019 [-6.198, 2.160] 0.343
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.347 [1.127, 9.567] 0.013*

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.593	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.387	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	9.803	14.399	19.675		
[95% CI]	[4.528, 15.079]	[9.672, 19.125]	[11.532, 27.817]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-4.595 [-11.689, 2.499] 0.203
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-9.871 [-19.571, -0.172] 0.046*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.276 [-4.142, 14.694] 0.271

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	13.847	17.563	21.087		
[95% CI]	[8.078, 19.617]	[12.395, 22.731]	[12.153, 30.021]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-3.716 [-11.472, 4.041] 0.346
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-7.239 [-17.873, 3.394] 0.181
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.524 [-6.799, 13.846] 0.502
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.906	19.945	23.779		
[95% CI]	[11.971, 23.841]	[14.602, 25.288]	[14.537, 33.021]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-2.039 [-10.035, 5.957] 0.616
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.873 [-16.856, 5.110] 0.293
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.834 [-6.842, 14.510] 0.480

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.710	21.663	20.325		
[95% CI]	[12.589, 24.831]	[16.138, 27.189]	[10.736, 29.914]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-2.953 [-11.210, 5.303] 0.482
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.615 [-12.991, 9.762] 0.780
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.338 [-12.405, 9.729] 0.812
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.943	23.649	21.045		
[95% CI]	[16.517, 29.369]	[17.820, 29.477]	[10.932, 31.158]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.706 [-9.392, 7.980] 0.873
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.898 [-10.086, 13.881] 0.755
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-2.604 [-14.275, 9.068] 0.661

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12a Statistical Analysis of Percentage of Rescue Medication-free days by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.411	18.359	22.319		
[95% CI]	[10.053, 20.768]	[13.551, 23.167]	[14.011, 30.627]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-2.948 [-10.157, 4.261] 0.421
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-6.909 [-16.793, 2.976] 0.170
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.960 [-5.640, 13.561] 0.417
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.037	20.469	21.488		
[95% CI]	[12.511, 23.564]	[15.497, 25.441]	[12.884, 30.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-2.432 [-9.876, 5.012] 0.521
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.451 [-13.676, 6.774] 0.507
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.019 [-8.919, 10.957] 0.840

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.537	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.218	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	6.958	11.190	13.482		
[95% CI]	[3.673, 10.244]	[8.122, 14.259]	[8.767, 18.198]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-4.232 [-8.727, 0.263] 0.065
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-6.524 [-12.273, -0.775] 0.026*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.292 [-3.335, 7.918] 0.424

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	12.565	12.368	15.272		
[95% CI]	[8.764, 16.366]	[8.816, 15.920]	[9.805, 20.738]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.197 [-5.004, 5.399] 0.941
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.706 [-9.366, 3.954] 0.425
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.903 [-3.616, 9.423] 0.382
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.346	12.823	15.962		
[95% CI]	[10.330, 18.363]	[9.065, 16.582]	[10.191, 21.733]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.523 [-3.977, 7.023] 0.587
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.616 [-8.649, 5.417] 0.652
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.139 [-3.749, 10.027] 0.371

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	15.468	12.785	17.411		
[95% CI]	[11.171, 19.765]	[8.761, 16.808]	[11.226, 23.595]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.684 [-3.202, 8.570] 0.371
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.942 [-9.475, 5.590] 0.613
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.626 [-2.753, 12.005] 0.219
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	17.037	13.612	17.856		
[95% CI]	[12.613, 21.461]	[9.472, 17.751]	[11.483, 24.230]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.426 [-2.632, 9.484] 0.267
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.819 [-8.579, 6.941] 0.836
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.245 [-3.356, 11.845] 0.273

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.662	12.432	15.368		
[95% CI]	[9.054, 16.270]	[9.059, 15.805]	[10.183, 20.553]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.230 [-4.709, 5.168] 0.927
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.707 [-9.025, 3.612] 0.401
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.936 [-3.250, 9.122] 0.352
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	14.427	12.799	16.492		
[95% CI]	[10.651, 18.203]	[9.266, 16.332]	[11.062, 21.922]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.628 [-3.543, 6.799] 0.537
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.065 [-8.681, 4.551] 0.540
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.693 [-2.786, 10.172] 0.263

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.248	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.744	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	12.532	11.231	14.310		
[95% CI]	[10.108, 14.955]	[8.689, 13.773]	[10.927, 17.692]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.301 [-2.213, 4.814] 0.468
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.778 [-5.944, 2.388] 0.402
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.079 [-1.152, 7.309] 0.154

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	15.900	15.850	18.220		
[95% CI]	[13.124, 18.677]	[12.939, 18.762]	[14.336, 22.104]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.050 [-3.974, 4.074] 0.981
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.320 [-7.100, 2.460] 0.341
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.370 [-2.483, 7.223] 0.338
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	20.170	17.645	22.544		
[95% CI]	[17.183, 23.157]	[14.516, 20.775]	[18.361, 26.727]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.524 [-1.803, 6.852] 0.253
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.374 [-7.520, 2.772] 0.365
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.899 [-0.325, 10.122] 0.066

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.938	18.419	22.752		
[95% CI]	[17.780, 24.097]	[15.106, 21.732]	[18.319, 27.186]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.519 [-2.059, 7.097] 0.280
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.814 [-7.264, 3.636] 0.514
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.333 [-1.200, 9.867] 0.125
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	21.647	18.865	23.055		
[95% CI]	[18.402, 24.891]	[15.463, 22.267]	[18.496, 27.613]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.782 [-1.920, 7.483] 0.246
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.408 [-7.010, 4.194] 0.622
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.190 [-1.497, 9.877] 0.149

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12b Statistical Analysis of Percentage of Rescue Medication-free days by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	17.681	16.106	19.947		
[95% CI]	[15.070, 20.292]	[13.368, 18.844]	[16.293, 23.600]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.575 [-2.209, 5.359] 0.414
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.266 [-6.761, 2.230] 0.323
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.841 [-0.724, 8.405] 0.099
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	19.473	17.365	21.419		
[95% CI]	[16.718, 22.228]	[14.477, 20.254]	[17.560, 25.279]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.108 [-1.885, 6.100] 0.300
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.946 [-6.694, 2.801] 0.421
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.054 [-0.766, 8.874] 0.099

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Bmi Class: < 25					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.026*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.077	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	10.558	9.742	16.052		
[95% CI]	[6.508, 14.607]	[5.859, 13.625]	[10.249, 21.855]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.816 [-4.798, 6.429] 0.775
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.494 [-12.575, 1.586] 0.128
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.310 [-0.670, 13.290] 0.076

Produced: 18 December 2020, 3:56

Page 1 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	15.228	12.338	17.340		
[95% CI]	[10.773, 19.684]	[8.073, 16.603]	[10.966, 23.714]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.890 [-3.281, 9.061] 0.358
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.112 [-9.893, 5.669] 0.594
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.002 [-2.664, 12.668] 0.200
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.889	12.494	24.407		
[95% CI]	[14.107, 23.670]	[7.932, 17.056]	[17.588, 31.226]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.394 [-0.218, 13.006] 0.058
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.519 [-13.852, 2.815] 0.194
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					11.913 [3.711, 20.114] 0.005**

Produced: 18 December 2020, 3:56

Page 2 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.094	13.785	25.193		
[95% CI]	[14.090, 24.098]	[9.016, 18.555]	[18.037, 32.349]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.308 [-1.608, 12.225] 0.132
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-6.100 [-14.837, 2.638] 0.171
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					11.408 [2.811, 20.005] 0.009**
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.393	12.939	26.639		
[95% CI]	[15.222, 25.563]	[8.016, 17.863]	[19.230, 34.047]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					7.453 [0.310, 14.597] 0.041*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-6.246 [-15.286, 2.794] 0.175
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					13.699 [4.807, 22.592] 0.003**

Produced: 18 December 2020, 3:56

Page 3 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	16.481	12.023	20.947		
[95% CI]	[12.261, 20.700]	[7.987, 16.059]	[14.916, 26.979]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.458 [-1.384, 10.300] 0.134
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.467 [-11.832, 2.899] 0.234
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.924 [1.670, 16.179] 0.016*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.087	12.709	23.404		
[95% CI]	[13.628, 22.546]	[8.451, 16.967]	[17.031, 29.777]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.378 [-0.791, 11.547] 0.087
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.317 [-13.099, 2.465] 0.180
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					10.695 [3.033, 18.357] 0.006**

Produced: 18 December 2020, 3:56

Page 4 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Bmi Class: [25-30)					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.737	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.990	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	11.459	12.525	13.726		
[95% CI]	[8.216, 14.702]	[9.164, 15.887]	[9.210, 18.243]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.066 [-5.737, 3.604] 0.654
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.267 [-7.829, 3.294] 0.424
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.201 [-4.431, 6.833] 0.675

Produced: 18 December 2020, 3:56

Page 5 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	15.537	16.804	18.821		
[95% CI]	[11.797, 19.277]	[12.930, 20.678]	[13.573, 24.068]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.267 [-6.652, 4.117] 0.644
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.284 [-9.729, 3.162] 0.317
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.016 [-4.509, 8.541] 0.544
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.980	19.496	20.597		
[95% CI]	[14.076, 21.885]	[15.434, 23.558]	[15.089, 26.106]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.516 [-7.150, 4.118] 0.597
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.617 [-9.371, 4.136] 0.447
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.101 [-5.746, 7.949] 0.752

Produced: 18 December 2020, 3:56

Page 6 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.250	19.599	20.803		
[95% CI]	[14.057, 22.443]	[15.223, 23.975]	[14.865, 26.740]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.349 [-7.409, 4.711] 0.662
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.552 [-9.823, 4.718] 0.491
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.204 [-6.177, 8.584] 0.749
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.847	20.675	20.593		
[95% CI]	[15.597, 24.098]	[16.236, 25.114]	[14.550, 26.635]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.828 [-6.973, 5.317] 0.791
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.745 [-8.135, 6.645] 0.843
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.082 [-7.585, 7.420] 0.983

Produced: 18 December 2020, 3:56

Page 7 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	16.225	17.595	18.994		
[95% CI]	[12.727, 19.724]	[13.966, 21.225]	[14.083, 23.904]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.370 [-6.411, 3.671] 0.594
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.768 [-8.799, 3.262] 0.368
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.398 [-4.711, 7.507] 0.653
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.606	18.845	19.850		
[95% CI]	[13.952, 21.261]	[15.045, 22.646]	[14.699, 25.000]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.239 [-6.511, 4.032] 0.644
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.243 [-8.560, 4.073] 0.486
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.004 [-5.400, 7.408] 0.758

Produced: 18 December 2020, 3:56

Page 8 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Bmi Class: >=30					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.621	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.457	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	9.270	11.094	12.918		
[95% CI]	[6.225, 12.316]	[8.044, 14.143]	[8.617, 17.220]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.823 [-6.134, 2.488] 0.406
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.648 [-8.917, 1.622] 0.174
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.825 [-3.449, 7.098] 0.497

Produced: 18 December 2020, 3:56

Page 9 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	13.245	13.594	15.306		
[95% CI]	[9.627, 16.864]	[9.962, 17.226]	[10.200, 20.411]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.349 [-5.477, 4.779] 0.894
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.060 [-8.317, 4.197] 0.518
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.711 [-4.555, 7.978] 0.592
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.196	14.226	17.045		
[95% CI]	[13.227, 21.166]	[10.246, 18.206]	[11.463, 22.628]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.970 [-2.652, 8.593] 0.300
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.151 [-6.698, 7.000] 0.965
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.819 [-4.038, 9.677] 0.420

Produced: 18 December 2020, 3:56

Page 10 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.324	14.279	17.950		
[95% CI]	[15.111, 23.537]	[10.058, 18.500]	[12.030, 23.870]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.045 [-0.920, 11.011] 0.097
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.374 [-5.891, 8.640] 0.710
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.671 [-3.602, 10.944] 0.322
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.536	15.590	18.137		
[95% CI]	[15.170, 23.902]	[11.221, 19.959]	[12.015, 24.258]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.946 [-2.232, 10.125] 0.210
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.399 [-6.119, 8.917] 0.715
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.547 [-4.975, 10.069] 0.506

Produced: 18 December 2020, 3:56

Page 11 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12c Statistical Analysis of Percentage of Rescue Medication-free days by Bmi (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	14.761	13.550	15.875		
[95% CI]	[11.306, 18.216]	[10.084, 17.016]	[11.004, 20.746]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.212 [-3.684, 6.107] 0.627
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.114 [-7.085, 4.858] 0.714
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.325 [-3.654, 8.305] 0.445
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.092	14.217	16.956		
[95% CI]	[13.445, 20.738]	[10.561, 17.873]	[11.823, 22.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.875 [-2.290, 8.040] 0.275
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.136 [-6.160, 6.432] 0.966
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.739 [-3.564, 9.042] 0.394

Produced: 18 December 2020, 3:56

Page 12 of 12

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.381	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.538	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	10.920	12.247	13.679		
[95% CI]	[8.788, 13.052]	[10.118, 14.375]	[10.672, 16.685]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.327 [-4.339, 1.686] 0.388
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.759 [-6.445, 0.927] 0.142
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.432 [-2.252, 5.116] 0.446

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.864	15.590	16.815		
[95% CI]	[12.405, 17.323]	[13.135, 18.045]	[13.338, 20.292]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.726 [-4.202, 2.749] 0.682
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.952 [-6.210, 2.307] 0.369
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.225 [-3.031, 5.481] 0.572
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.452	16.929	20.775		
[95% CI]	[15.829, 21.075]	[14.307, 19.550]	[17.066, 24.485]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.523 [-2.185, 5.232] 0.421
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.324 [-6.867, 2.220] 0.316
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.847 [-0.695, 8.389] 0.097

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.476	17.483	21.432		
[95% CI]	[16.697, 22.254]	[14.704, 20.261]	[17.498, 25.366]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.993 [-1.937, 5.923] 0.320
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.957 [-6.773, 2.860] 0.426
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.950 [-0.866, 8.766] 0.108
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.435	18.389	21.816		
[95% CI]	[17.589, 23.281]	[15.543, 21.234]	[17.782, 25.850]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.046 [-1.978, 6.071] 0.319
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.381 [-6.318, 3.556] 0.583
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.427 [-1.509, 8.363] 0.173

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	16.189	15.796	18.465		
[95% CI]	[13.874, 18.504]	[13.484, 18.109]	[15.193, 21.737]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.393 [-2.880, 3.665] 0.814
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.276 [-6.284, 1.732] 0.265
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.669 [-1.338, 6.675] 0.192
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.054	16.849	20.037		
[95% CI]	[15.622, 20.486]	[14.418, 19.279]	[16.597, 23.478]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.205 [-2.234, 4.644] 0.492
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.983 [-6.197, 2.230] 0.356
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.189 [-1.024, 7.401] 0.138

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.019*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.797	
Baseline				<0.001***	
Baseline*Inter-Visit Period				0.018*	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	7.429	4.867	16.532		
[95% CI]	[2.647, 12.212]	[-0.030, 9.765]	[9.781, 23.284]		
p-value	0.002**	0.051	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.562 [-4.281, 9.405] 0.461
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-9.103 [-17.395, -0.812] 0.032*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					11.665 [3.319, 20.011] 0.006**

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	12.976	6.856	20.128		
[95% CI]	[7.637, 18.316]	[1.389, 12.324]	[12.591, 27.665]		
p-value	<0.001***	0.014*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.120 [-1.519, 13.760] 0.116
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-7.151 [-16.408, 2.105] 0.129
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					13.272 [3.954, 22.589] 0.005**
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	14.342	7.423	18.804		
[95% CI]	[8.513, 20.172]	[1.475, 13.372]	[10.575, 27.034]		
p-value	<0.001***	0.015*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.919 [-1.406, 15.245] 0.103
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.462 [-14.572, 5.648] 0.385
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					11.381 [1.220, 21.542] 0.028*

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	14.575	7.060	19.148		
[95% CI]	[8.328, 20.821]	[0.669, 13.451]	[10.234, 28.063]		
p-value	<0.001***	0.031*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					7.515 [-1.417, 16.446] 0.099
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.574 [-15.493, 6.345] 0.410
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					12.088 [1.110, 23.067] 0.031*
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	15.880	5.725	19.698		
[95% CI]	[9.375, 22.385]	[-0.897, 12.346]	[10.442, 28.954]		
p-value	<0.001***	0.090	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					10.155 [0.879, 19.432] 0.032*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.818 [-15.168, 7.533] 0.508
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					13.973 [2.581, 25.365] 0.016*

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12d Statistical Analysis of Percentage of Rescue Medication-free days by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	12.859	6.856	18.862		
[95% CI]	[7.681, 18.036]	[1.560, 12.151]	[11.553, 26.171]		
p-value	<0.001***	0.011*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					6.003 [-1.401, 13.407] 0.111
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-6.004 [-14.981, 2.974] 0.189
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					12.007 [2.975, 21.038] 0.009**
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	14.018	6.650	19.132		
[95% CI]	[8.589, 19.447]	[1.102, 12.197]	[11.446, 26.819]		
p-value	<0.001***	0.019*	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					7.368 [-0.391, 15.127] 0.063
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.114 [-14.549, 4.320] 0.286
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					12.482 [2.996, 21.969] 0.010*

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	439	451	229		
Effect					
Treatment				0.550	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.484	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	10.942	11.920	13.261		
[95% CI]	[8.723, 13.161]	[9.725, 14.115]	[10.190, 16.331]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.978 [-4.099, 2.143] 0.539
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.319 [-6.107, 1.469] 0.230
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.341 [-2.433, 5.115] 0.486

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.716	14.958	15.660		
[95% CI]	[12.180, 17.253]	[12.446, 17.470]	[12.145, 19.176]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.242 [-3.812, 3.329] 0.894
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.944 [-5.279, 3.391] 0.669
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.702 [-3.618, 5.023] 0.750
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.092	16.061	19.081		
[95% CI]	[15.372, 20.812]	[13.367, 18.755]	[15.308, 22.853]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.031 [-1.798, 5.860] 0.298
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.989 [-5.640, 3.662] 0.677
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.020 [-1.616, 7.655] 0.202

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.157	16.536	19.337		
[95% CI]	[16.276, 22.037]	[13.682, 19.390]	[15.331, 23.344]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.621 [-1.434, 6.675] 0.205
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.181 [-5.115, 4.754] 0.943
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.802 [-2.117, 7.720] 0.264
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	20.076	16.933	19.596		
[95% CI]	[17.089, 23.063]	[13.972, 19.893]	[15.436, 23.755]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.143 [-1.063, 7.349] 0.143
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.480 [-4.641, 5.602] 0.854
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.663 [-2.443, 7.769] 0.306

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.953	15.084	17.133		
[95% CI]	[13.556, 18.351]	[12.710, 17.458]	[13.810, 20.455]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.869 [-2.505, 4.243] 0.613
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.180 [-5.277, 2.918] 0.572
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.048 [-2.035, 6.132] 0.325
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.767	15.902	18.295		
[95% CI]	[15.236, 20.298]	[13.395, 18.409]	[14.782, 21.807]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.865 [-1.697, 5.428] 0.304
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.528 [-4.857, 3.802] 0.811
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.393 [-1.922, 6.708] 0.277

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.025*	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.977	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	8.685	8.673	17.198		
[95% CI]	[4.563, 12.807]	[4.360, 12.987]	[10.985, 23.411]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-5.963, 5.987] 0.997
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-8.513 [-15.985, -1.040] 0.026*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.525 [0.970, 16.079] 0.027*

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.293	12.285	23.379		
[95% CI]	[9.461, 19.124]	[7.245, 17.325]	[16.061, 30.697]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.007 [-4.985, 9.000] 0.573
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-9.086 [-17.875, -0.297] 0.043*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					11.094 [2.219, 19.969] 0.014*
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.234	14.018	25.344		
[95% CI]	[12.057, 22.412]	[8.614, 19.422]	[17.507, 33.181]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.216 [-4.278, 10.711] 0.399
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-8.110 [-17.524, 1.304] 0.091
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					11.326 [1.818, 20.834] 0.020*

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	17.653	14.313	27.268		
[95% CI]	[12.125, 23.182]	[8.532, 20.094]	[18.915, 35.621]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.340 [-4.669, 11.350] 0.412
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-9.614 [-19.655, 0.426] 0.060
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					12.955 [2.808, 23.102] 0.013*
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.075	15.738	27.978		
[95% CI]	[13.568, 24.582]	[10.001, 21.475]	[19.665, 36.291]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.337 [-4.626, 11.300] 0.410
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-8.903 [-18.899, 1.093] 0.081
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					12.240 [2.150, 22.330] 0.018*

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12e Statistical Analysis of Percentage of Rescue Medication-free days by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.014	12.663	23.486		
[95% CI]	[10.425, 19.603]	[7.872, 17.453]	[16.543, 30.430]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.351 [-4.292, 8.995] 0.487
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-8.472 [-16.814, -0.131] 0.047*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					10.824 [2.398, 19.249] 0.012*
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.662	13.817	25.541		
[95% CI]	[11.896, 21.428]	[8.840, 18.793]	[18.331, 32.751]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.845 [-4.055, 9.745] 0.418
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-8.879 [-17.542, -0.217] 0.045*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					11.724 [2.974, 20.474] 0.009**

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.327	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.474	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	9.381	12.181	15.237		
[95% CI]	[6.660, 12.102]	[9.364, 14.999]	[11.364, 19.111]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-2.801 [-6.721, 1.120] 0.161
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.856 [-10.594, -1.119] 0.015*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.056 [-1.731, 7.843] 0.211

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	13.543	15.510	18.830		
[95% CI]	[10.407, 16.679]	[12.257, 18.763]	[14.346, 23.314]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.966 [-6.489, 2.556] 0.394
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.286 [-10.763, 0.190] 0.058
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.320 [-2.217, 8.857] 0.239
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.191	15.845	19.717		
[95% CI]	[13.769, 20.613]	[12.298, 19.392]	[14.820, 24.613]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.346 [-3.587, 6.279] 0.592
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.526 [-8.504, 3.453] 0.407
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.872 [-2.172, 9.915] 0.209

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	17.898	15.325	19.624		
[95% CI]	[14.255, 21.542]	[11.549, 19.101]	[14.404, 24.844]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.573 [-2.678, 7.825] 0.336
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.726 [-8.097, 4.646] 0.595
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.299 [-2.141, 10.738] 0.190
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	18.166	15.229	19.619		
[95% CI]	[14.427, 21.905]	[11.354, 19.104]	[14.250, 24.987]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.937 [-2.451, 8.325] 0.285
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.453 [-8.001, 5.095] 0.663
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.390 [-2.228, 11.007] 0.193

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	14.867	15.178	18.755		
[95% CI]	[11.879, 17.856]	[12.080, 18.277]	[14.484, 23.026]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.311 [-4.619, 3.997] 0.887
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.888 [-9.104, 1.329] 0.144
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.576 [-1.697, 8.850] 0.183
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	16.445	15.230	19.188		
[95% CI]	[13.270, 19.619]	[11.939, 18.520]	[14.646, 23.731]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.215 [-3.361, 5.791] 0.602
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.744 [-8.290, 2.803] 0.332
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.959 [-1.648, 9.565] 0.166

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.214	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.717	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	11.559	10.325	12.830		
[95% CI]	[8.737, 14.381]	[7.597, 13.052]	[8.904, 16.755]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.234 [-2.691, 5.160] 0.537
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.271 [-6.105, 3.564] 0.606
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.505 [-2.275, 7.286] 0.304

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1)
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	15.790	13.322	15.543		
[95% CI]	[12.557, 19.023]	[10.202, 16.442]	[11.045, 20.041]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.468 [-2.025, 6.962] 0.281
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.247 [-5.292, 5.786] 0.930
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.221 [-3.253, 7.695] 0.426
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.702	15.414	20.938		
[95% CI]	[15.300, 22.104]	[12.126, 18.702]	[16.205, 25.670]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.288 [-1.444, 8.020] 0.173
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.236 [-8.064, 3.593] 0.452
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.523 [-0.239, 11.286] 0.060

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.808	16.797	22.299		
[95% CI]	[16.218, 23.398]	[13.323, 20.272]	[17.291, 27.308]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.011 [-1.986, 8.007] 0.237
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.491 [-8.653, 3.670] 0.428
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.502 [-0.594, 11.598] 0.077
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	21.675	18.101	23.098		
[95% CI]	[17.995, 25.355]	[14.543, 21.658]	[17.969, 28.226]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.574 [-1.544, 8.693] 0.171
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.423 [-7.735, 4.889] 0.658
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.997 [-1.245, 11.239] 0.116

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12f Statistical Analysis of Percentage of Rescue Medication-free days by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	16.707	13.987	18.030		
[95% CI]	[13.668, 19.746]	[11.052, 16.923]	[13.803, 22.258]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.720 [-1.506, 6.946] 0.207
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.323 [-6.530, 3.883] 0.618
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.043 [-1.104, 9.190] 0.123
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.688	15.693	20.349		
[95% CI]	[15.530, 21.847]	[12.641, 18.745]	[15.952, 24.746]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.995 [-1.397, 7.388] 0.181
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.661 [-7.074, 3.753] 0.547
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.656 [-0.697, 10.009] 0.088

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.156	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.168	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	12.153	9.398	16.321		
[95% CI]	[7.992, 16.314]	[5.360, 13.436]	[10.827, 21.815]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.755 [-3.043, 8.553] 0.351
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.169 [-11.061, 2.724] 0.235
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.924 [0.105, 13.742] 0.047*

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	16.074	13.342	17.815		
[95% CI]	[11.212, 20.937]	[8.624, 18.060]	[11.387, 24.243]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.733 [-4.043, 9.508] 0.428
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.741 [-9.801, 6.319] 0.671
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.474 [-3.500, 12.447] 0.271
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.236	13.257	19.403		
[95% CI]	[12.157, 22.315]	[8.330, 18.184]	[12.701, 26.105]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.979 [-3.097, 11.056] 0.269
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.167 [-10.576, 6.242] 0.613
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.146 [-2.172, 14.465] 0.147

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	20.321	12.839	19.099		
[95% CI]	[15.185, 25.457]	[7.848, 17.831]	[12.319, 25.880]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					7.482 [0.319, 14.644] 0.041*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.222 [-7.285, 9.728] 0.778
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.260 [-2.160, 14.680] 0.145
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.536	14.237	23.118		
[95% CI]	[14.082, 24.990]	[8.933, 19.542]	[15.915, 30.320]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					5.299 [-2.310, 12.907] 0.172
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.582 [-12.616, 5.453] 0.436
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.880 [-0.065, 17.825] 0.052

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	16.097	12.689	18.440		
[95% CI]	[11.541, 20.652]	[8.269, 17.110]	[12.423, 24.458]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.407 [-2.941, 9.755] 0.292
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.344 [-9.891, 5.204] 0.542
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.751 [-1.715, 13.217] 0.131
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	18.028	13.087	19.697		
[95% CI]	[13.376, 22.679]	[8.572, 17.602]	[13.555, 25.839]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.941 [-1.542, 11.423] 0.135
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.670 [-9.374, 6.035] 0.670
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.610 [-1.013, 14.233] 0.089

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.334	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.195	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	9.924	11.805	13.249		
[95% CI]	[7.710, 12.138]	[9.565, 14.045]	[10.061, 16.436]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.881 [-5.032, 1.269] 0.242
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.325 [-7.207, 0.558] 0.093
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.443 [-2.452, 5.339] 0.467

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.189	14.722	16.994		
[95% CI]	[11.655, 16.722]	[12.158, 17.286]	[13.338, 20.650]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.533 [-4.138, 3.072] 0.772
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.805 [-7.255, 1.645] 0.216
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.272 [-2.192, 6.737] 0.318
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.111	16.365	20.621		
[95% CI]	[15.374, 20.849]	[13.593, 19.136]	[16.666, 24.576]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.746 [-2.150, 5.643] 0.379
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.510 [-7.321, 2.302] 0.306
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.256 [-0.572, 9.084] 0.084

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.397	17.052	21.518		
[95% CI]	[15.453, 21.340]	[14.072, 20.033]	[17.256, 25.781]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.344 [-2.845, 5.534] 0.529
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.122 [-8.304, 2.061] 0.237
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.466 [-0.735, 9.666] 0.092
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.951	17.395	20.601		
[95% CI]	[16.953, 22.949]	[14.361, 20.429]	[16.254, 24.949]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.556 [-1.710, 6.822] 0.240
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.650 [-5.934, 4.633] 0.809
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.206 [-2.094, 8.507] 0.236

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12g Statistical Analysis of Percentage of Rescue Medication-free days by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.645	15.158	18.371		
[95% CI]	[13.240, 18.050]	[12.724, 17.592]	[14.901, 21.841]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.487 [-2.935, 3.909] 0.780
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.726 [-6.950, 1.498] 0.206
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.213 [-1.025, 7.451] 0.137
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.379	16.184	19.733		
[95% CI]	[14.827, 19.932]	[13.600, 18.768]	[16.044, 23.422]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.195 [-2.438, 4.828] 0.519
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.354 [-6.841, 2.134] 0.304
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.549 [-0.954, 8.052] 0.122

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.725	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.601	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	11.138	12.054	14.778		
[95% CI]	[8.261, 14.016]	[9.243, 14.866]	[10.671, 18.884]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.916 [-4.941, 3.108] 0.655
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.640 [-8.654, 1.375] 0.155
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.723 [-2.253, 7.700] 0.283

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.288	14.646	17.344		
[95% CI]	[11.050, 17.525]	[11.481, 17.812]	[12.732, 21.957]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.358 [-4.887, 4.171] 0.877
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.056 [-8.692, 2.579] 0.287
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.698 [-2.896, 8.292] 0.344
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	17.668	15.846	18.561		
[95% CI]	[14.200, 21.136]	[12.448, 19.243]	[13.617, 23.505]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.822 [-3.034, 6.679] 0.461
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.893 [-6.932, 5.146] 0.772
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.715 [-3.283, 8.714] 0.374

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	19.121	16.372	17.302		
[95% CI]	[15.411, 22.832]	[12.733, 20.011]	[12.013, 22.591]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.749 [-2.449, 7.948] 0.299
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.820 [-4.641, 8.281] 0.580
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.930 [-5.490, 7.349] 0.776
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.821	16.723	17.382		
[95% CI]	[15.920, 23.722]	[12.897, 20.550]	[11.833, 22.931]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.098 [-2.367, 8.563] 0.266
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.439 [-4.344, 9.222] 0.480
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.659 [-6.081, 7.398] 0.848

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.623	14.893	17.605		
[95% CI]	[12.566, 18.681]	[11.902, 17.885]	[13.246, 21.963]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.730 [-3.549, 5.009] 0.738
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.981 [-7.306, 3.343] 0.465
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.711 [-2.575, 7.998] 0.314
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.534	15.714	17.472		
[95% CI]	[14.305, 20.763]	[12.551, 18.876]	[12.869, 22.074]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.820 [-2.701, 6.341] 0.430
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.062 [-5.560, 5.685] 0.983
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.758 [-3.826, 7.342] 0.537

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.093	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.337	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	9.742	10.450	13.344		
[95% CI]	[7.078, 12.407]	[7.714, 13.187]	[9.626, 17.062]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.708 [-4.528, 3.112] 0.716
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.602 [-8.178, 0.974] 0.123
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.894 [-1.723, 7.511] 0.219

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and

baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.893	14.253	16.932		
[95% CI]	[11.776, 18.009]	[11.054, 17.452]	[12.560, 21.304]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.640 [-3.826, 5.105] 0.779
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.039 [-7.410, 3.331] 0.456
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.679 [-2.739, 8.097] 0.332
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	18.089	15.548	21.676		
[95% CI]	[14.753, 21.424]	[12.129, 18.967]	[16.998, 26.353]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.540 [-2.236, 7.316] 0.297
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.587 [-9.334, 2.160] 0.221
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.127 [0.332, 11.922] 0.038*

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	18.503	15.888	24.043		
[95% CI]	[14.996, 22.009]	[12.292, 19.484]	[19.107, 28.978]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.615 [-2.407, 7.637] 0.307
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.540 [-11.596, 0.516] 0.073
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.155 [2.047, 14.262] 0.009**
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	19.823	16.714	24.763		
[95% CI]	[16.304, 23.343]	[13.108, 20.320]	[19.795, 29.731]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.109 [-1.929, 8.147] 0.226
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.940 [-11.031, 1.151] 0.112
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					8.049 [1.909, 14.189] 0.010*

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12h Statistical Analysis of Percentage of Rescue Medication-free days by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	15.821	14.366	18.934		
[95% CI]	[12.869, 18.773]	[11.337, 17.395]	[14.798, 23.071]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.456 [-2.774, 5.685] 0.499
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-3.113 [-8.197, 1.970] 0.230
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.569 [-0.559, 9.697] 0.081
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	17.467	15.317	21.655		
[95% CI]	[14.378, 20.555]	[12.149, 18.485]	[17.319, 25.990]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.149 [-2.275, 6.573] 0.341
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.188 [-9.513, 1.137] 0.123
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.337 [0.967, 11.708] 0.021*

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.338	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.345	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	9.862	10.452	12.311		
[95% CI]	[7.485, 12.240]	[8.066, 12.837]	[8.954, 15.668]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.589 [-3.959, 2.780] 0.731
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.449 [-6.563, 1.665] 0.243
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.859 [-2.258, 5.977] 0.376

Produced: 18 December 2020, 3:56

Page 1 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	14.194	12.998	14.514		
[95% CI]	[11.476, 16.912]	[10.271, 15.724]	[10.672, 18.356]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.196 [-2.655, 5.047] 0.542
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.320 [-5.027, 4.386] 0.894
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.516 [-3.194, 6.227] 0.528
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	16.307	13.965	17.183		
[95% CI]	[13.342, 19.272]	[10.995, 16.935]	[12.992, 21.374]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.342 [-1.855, 6.540] 0.274
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.876 [-6.010, 4.258] 0.738
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.218 [-1.918, 8.354] 0.219

Produced: 18 December 2020, 3:56

Page 2 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	15.986	14.263	18.886		
[95% CI]	[12.841, 19.132]	[11.112, 17.415]	[14.431, 23.341]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.723 [-2.732, 6.177] 0.448
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.900 [-8.354, 2.554] 0.297
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.623 [-0.834, 10.080] 0.097
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	17.422	14.053	19.167		
[95% CI]	[14.156, 20.688]	[10.783, 17.323]	[14.534, 23.799]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.369 [-1.254, 7.992] 0.153
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.744 [-7.413, 3.924] 0.546
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.113 [-0.556, 10.783] 0.077

Produced: 18 December 2020, 3:56

Page 3 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	14.665	13.127	15.613		
[95% CI]	[12.064, 17.267]	[10.519, 15.735]	[11.937, 19.288]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.539 [-2.146, 5.223] 0.413
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.947 [-5.450, 3.556] 0.680
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.486 [-2.021, 6.992] 0.279
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	15.657	13.647	17.314		
[95% CI]	[12.919, 18.395]	[10.903, 16.390]	[13.442, 21.186]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.011 [-1.867, 5.888] 0.309
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.657 [-6.400, 3.086] 0.493
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					3.667 [-1.078, 8.413] 0.130

Produced: 18 December 2020, 3:56

Page 4 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
Percentage of Days without Intake of Rescue Medication					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.269	
Inter-Visit Period				<0.001***	
Treatment*Inter-Visit Period				0.337	
Baseline				<0.001***	
Baseline*Inter-Visit Period				<0.001***	
Visit 2 - Visit 3 (Weeks 1-4)					
Adjusted Mean	11.151	12.151	16.257		
[95% CI]	[7.907, 14.396]	[8.903, 15.398]	[11.689, 20.824]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.999 [-5.589, 3.590] 0.669
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.105 [-10.709, 0.498] 0.074
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.106 [-1.499, 9.711] 0.151

Produced: 18 December 2020, 3:56

Page 5 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 3 - Visit 4 (Weeks 5-12)					
Adjusted Mean	15.180	16.086	20.611		
[95% CI]	[11.449, 18.912]	[12.350, 19.821]	[15.341, 25.880]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.905 [-6.185, 4.374] 0.736
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-5.430 [-11.889, 1.029] 0.099
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.525 [-1.936, 10.985] 0.170
Visit 4 - Visit 5 (Weeks 13-26)					
Adjusted Mean	19.929	17.657	24.261		
[95% CI]	[15.980, 23.877]	[13.695, 21.620]	[18.682, 29.840]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.272 [-3.322, 7.865] 0.425
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.332 [-11.169, 2.504] 0.214
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					6.604 [-0.241, 13.448] 0.059

Produced: 18 December 2020, 3:56

Page 6 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Visit 5 - Visit 6 (Weeks 27-40)					
Adjusted Mean	22.408	18.241	23.497		
[95% CI]	[18.217, 26.598]	[14.030, 22.452]	[17.564, 29.431]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					4.167 [-1.774, 10.107] 0.169
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.090 [-8.356, 6.176] 0.768
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.256 [-2.022, 12.534] 0.157
Visit 6 - Visit 7 (Weeks 41-52)					
Adjusted Mean	22.979	19.854	24.025		
[95% CI]	[18.714, 27.245]	[15.568, 24.140]	[17.982, 30.067]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					3.125 [-2.921, 9.171] 0.310
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.045 [-8.444, 6.353] 0.782
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					4.170 [-3.240, 11.581] 0.270

Produced: 18 December 2020, 3:56

Page 7 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

Table 22.2.12i Statistical Analysis of Percentage of Rescue Medication-free days by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Percentage of Days without Intake of Rescue Medication					
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	17.117	16.327	21.906		
[95% CI]	[13.617, 20.618]	[12.819, 19.834]	[16.964, 26.849]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.791 [-4.164, 5.746] 0.754
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-4.789 [-10.847, 1.269] 0.121
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.580 [-0.482, 11.642] 0.071
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	19.894	17.656	22.824		
[95% CI]	[16.212, 23.577]	[13.962, 21.350]	[17.619, 28.028]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.238 [-2.977, 7.454] 0.400
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.929 [-9.306, 3.448] 0.367
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					5.167 [-1.217, 11.551] 0.112

Produced: 18 December 2020, 3:56

Page 8 of 8

Source: Listing 16.2.6.5

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected inter-visit period

ADDITIONAL_TLF_BATCH3_HEALTH_ECONOMICS

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch3

Date of Production: 18/12/2020

Identification Code: Additional_TLF_batch3_Health_Economics_CCD-05993AB2-02_20201218(Batch3)

Table 25.2.11a Total Number Of Hospital Admissions Due To Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.957
Age Group			0.752
Age Group Treatment Interaction			0.775

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11b Total Number Of Hospital Admissions Due To Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.889
Gender			0.173
Gender Treatment Interaction			0.842

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11c Total Number Of Hospital Admissions Due To Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.665
Number of Asthma Exacerbations in Previous Year (1, >1)			0.193
BMI Class			0.510
BMI Class Treatment Interaction			0.794

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11d Total Number Of Hospital Admissions Due To Asthma including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			1.000
Smoking Status			1.000
Smoking Status Treatment Interaction			1.000

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11e Total Number Of Hospital Admissions Due To Asthma including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.597
Number of Exacerbation in the Previous year			0.497
Number of Exacerbation in the Previous year Treatment Interaction			0.482

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11f Total Number Of Hospital Admissions Due To Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	568	285	
Effect			
Treatment			0.848
Number of Asthma Exacerbations in Previous Year (1, >1)			0.179
Degree of reversibility at screening (delta FEV1)			0.766
Degree of reversibility at screening (delta FEV1) Treatment Interaction			0.272

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11g Total Number Of Hospital Admissions Due To Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.937
Use of spacer			0.412
Use of spacer Treatment Interaction			0.146

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11h Total Number Of Hospital Admissions Due To Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.645
Number of Asthma Exacerbations in Previous Year (1, >1)			0.155
Relevant Concomitant Cardiovascular Disease			0.067
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.567

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11i Total Number Of Hospital Admissions Due To Asthma including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.860
Number of Asthma Exacerbations in Previous Year (1, >1)			0.192
Region			0.928
Region Treatment Interaction			0.310

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11a1 Total Number Of Hospital Admissions Due To Asthma stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group:<65 years old					
Number of Patients Included in Model	472	444	244		
Effect					
Treatment				0.815	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.223	
Adjusted Rate per Patient per Year [95% CI]	0.021 [0.011, 0.040]	0.016 [0.007, 0.033]	0.017 [0.006, 0.044]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.348 [0.513, 3.542] 0.544
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.267 [0.397, 4.042] 0.689
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.064 [0.311, 3.635] 0.921

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11a1 Total Number Of Hospital Admissions Due To Asthma stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	97	121	41		
Effect					
Treatment				0.900	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.379	
Adjusted Rate per Patient per Year [95% CI]	0.010 [0.000, 0.425]	0.025 [0.002, 0.293]	0.039 [0.001, 1.677]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.403 [0.002, 65.43] 0.727
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.256 [0.001, 87.87] 0.647
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.576 [0.022, 112.2] 0.834

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11b1 Total Number Of Hospital Admissions Due To Asthma stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	242	101		
Effect					
Treatment				0.949	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.912	
Adjusted Rate per Patient per Year [95% CI]	0.010 [0.002, 0.039]	0.013 [0.004, 0.040]	0.010 [0.001, 0.072]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.759 [0.127, 4.543]
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.961 [0.087, 10.60]
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.790 [0.082, 7.598]

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11b1 Total Number Of Hospital Admissions Due To Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	357	323	184		
Effect					
Treatment				0.779	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.133	
Adjusted Rate per Patient per Year [95% CI]	0.027 [0.013, 0.055]	0.018 [0.008, 0.044]	0.022 [0.008, 0.066]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.494 [0.489, 4.562] 0.481
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.214 [0.335, 4.402] 0.768
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.231 [0.307, 4.928] 0.769

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11d1 Total Number Of Hospital Admissions Due To Asthma stratified by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	486	486	243		
Effect					
Treatment				0.563	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.172	
Adjusted Rate per Patient per Year [95% CI]	0.024 [0.013, 0.046]	0.014 [0.006, 0.032]	0.017 [0.006, 0.048]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.700 [0.618, 4.679] 0.304
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.471 [0.430, 5.035] 0.538
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.156 [0.309, 4.325] 0.830

Produced: 18 December 2020, 5:17
Source: Listing 16.2.6.7.3

Page 1 of 1

Table 25.2.11e1 Total Number Of Hospital Admissions Due To Asthma stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.718	
Adjusted Rate per Patient per Year [95% CI]	0.042 [0.015, 0.119]	0.026 [0.007, 0.091]	0.018 [0.002, 0.151]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.638 [0.320, 8.384] 0.554
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.326 [0.220, 24.61] 0.483
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.704 [0.060, 8.292] 0.781

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.11g1 Total Number Of Hospital Admissions Due To Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	128	137	74		
Effect					
Treatment				0.552	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.267	
Adjusted Rate per Patient per Year [95% CI]	0.015 [0.004, 0.061]	0.021 [0.006, 0.066]	0.039 [0.012, 0.123]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.726 [0.121, 4.344] 0.725
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.388 [0.065, 2.322] 0.300
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.870 [0.377, 9.265] 0.443

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11g1 Total Number Of Hospital Admissions Due To Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	441	428	211		
Effect					
Treatment				0.526	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.402	
Adjusted Rate per Patient per Year [95% CI]	0.023 [0.011, 0.048]	0.014 [0.006, 0.035]	0.010 [0.002, 0.045]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.617 [0.517, 5.062] 0.409
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.281 [0.436, 11.92] 0.328
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.709 [0.126, 3.988] 0.696

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11h1 Total Number Of Hospital Admissions Due To Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	284	134		
Effect					
Treatment				0.775	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.667	
Adjusted Rate per Patient per Year [95% CI]	0.030 [0.015, 0.060]	0.022 [0.010, 0.048]	0.032 [0.012, 0.084]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.375 [0.475, 3.985] 0.557
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.916 [0.281, 2.983] 0.884
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.502 [0.432, 5.224] 0.522

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11h1 Total Number Of Hospital Admissions Due To Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	296	281	151		
Effect Treatment				0.828	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.025*	
Adjusted Rate per Patient per Year [95% CI]	0.010 [0.003, 0.032]	0.008 [0.002, 0.028]	0.005 [0.001, 0.040]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.287 [0.288, 5.751] 0.741
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.937 [0.216, 17.33] 0.554
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.664 [0.069, 6.389] 0.723

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11i1 Total Number Of Hospital Admissions Due To Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	317	315	159		
Effect					
Treatment				0.637	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.256	
Adjusted Rate per Patient per Year [95% CI]	0.026 [0.011, 0.060]	0.015 [0.006, 0.042]	0.013 [0.003, 0.061]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.674 [0.456, 6.151] 0.438
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.969 [0.341, 11.36] 0.449
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.850 [0.135, 5.342] 0.863

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.11i1 Total Number Of Hospital Admissions Due To Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	250	126		
Effect					
Treatment				0.790	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.298	
Adjusted Rate per Patient per Year [95% CI]	0.015 [0.006, 0.042]	0.016 [0.006, 0.042]	0.025 [0.008, 0.077]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.985 [0.246, 3.940] 0.983
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.622 [0.139, 2.794] 0.536
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.583 [0.353, 7.107] 0.549

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12a Total Number Of Hospital Days Due To Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.690
Number of Asthma Exacerbations in Previous Year (1, >1)			0.352
Age Group			0.728
Age Group Treatment Interaction			0.629

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12b Total Number Of Hospital Days Due To Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.938
Gender			0.554
Gender Treatment Interaction			0.759

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effects and log-time on study as an offset

Table 25.2.12c Total Number Of Hospital Days Due To Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.986
Number of Asthma Exacerbations in Previous Year (1, >1)			0.299
BMI Class			0.690
BMI Class Treatment Interaction			0.877

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12e Total Number Of Hospital Days Due To Asthma including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.910
Number of Exacerbation in the Previous year			0.446
Number of Exacerbation in the Previous year Treatment Interaction			0.682

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effects and log-time on study as an offset

Table 25.2.12f Total Number Of Hospital Days Due To Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	568	285	
Effect			
Treatment			0.596
Number of Asthma Exacerbations in Previous Year (1, >1)			0.127
Degree of reversibility at screening (delta FEV1)			0.490
Degree of reversibility at screening (delta FEV1) Treatment Interaction			0.384

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12g Total Number Of Hospital Days Due To Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.857
Number of Asthma Exacerbations in Previous Year (1, >1)			0.379
Use of spacer			0.405
Use of spacer Treatment Interaction			0.351

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12h Total Number Of Hospital Days Due To Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.775
Number of Asthma Exacerbations in Previous Year (1, >1)			0.097
Relevant Concomitant Cardiovascular Disease			0.047*
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.445

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12i Total Number Of Hospital Days Due To Asthma including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.951
Number of Asthma Exacerbations in Previous Year (1, >1)			0.350
Region			0.522
Region Treatment Interaction			0.607

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12a1 Total Number Of Hospital Days Due To Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group:<65 years old					
Number of Patients Included in Model	472	444	244		
Effect					
Treatment				0.992	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.487	
Adjusted Rate per Patient per Year [95% CI]	0.158 [0.048, 0.520]	0.145 [0.042, 0.494]	0.141 [0.027, 0.742]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.094 [0.198, 6.041] 0.918
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.122 [0.146, 8.634] 0.912
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.975 [0.124, 7.688] 0.981

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12a1 Total Number Of Hospital Days Due To Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	97	121	41		
Effect					
Treatment				0.497	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.197	
Adjusted Rate per Patient per Year [95% CI]	0.008 [0.000, 2.825]	0.665 [0.026, 16.68]	1.085 [0.007, 163.6]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.012 [0.000, 27.75] 0.263
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.007 [0.000, 41.83] 0.265
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.633 [0.007, 393.5] 0.861

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12b1 Total Number Of Hospital Days Due To Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	242	101		
Effect					
Treatment				0.947	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.712	
Adjusted Rate per Patient per Year [95% CI]	0.087 [0.008, 0.927]	0.153 [0.015, 1.517]	0.129 [0.005, 3.632]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.566 [0.017, 18.49] 0.749
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.671 [0.013, 35.40] 0.844
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.843 [0.013, 56.77] 0.937

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12b1 Total Number Of Hospital Days Due To Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	357	323	184		
Effect					
Treatment				0.994	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.293	
Adjusted Rate per Patient per Year [95% CI]	0.182 [0.048, 0.697]	0.204 [0.051, 0.823]	0.192 [0.031, 1.172]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.893 [0.122, 6.522] 0.911
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.951 [0.098, 9.212] 0.965
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.939 [0.097, 9.086] 0.957

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.19.2d Total Number Of Hospital Days Due To Asthma stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.909	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.356	
Adjusted Rate per Patient per Year [95% CI]	0.102 [0.012, 0.874]	0.138 [0.018, 1.029]	0.050 [0.001, 2.564]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.740 [0.044, 12.51] 0.835
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.061 [0.016, 264.3] 0.770
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.359 [0.003, 40.95] 0.672

Produced: 18 December 2020, 5:17

Page 1 of 3

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.19.2d Total Number Of Hospital Days Due To Asthma stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	216	200	110		
Effect					
Treatment				0.923	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.891	
Adjusted Rate per Patient per Year [95% CI]	0.189 [0.023, 1.593]	0.152 [0.018, 1.299]	0.088 [0.005, 1.722]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.245 [0.057, 27.26] 0.889
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.148 [0.050, 93.02] 0.691
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.580 [0.016, 21.33] 0.767

Produced: 18 December 2020, 5:17

Page 2 of 3

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.19.2d Total Number Of Hospital Days Due To Asthma stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	203	202	102		
Effect					
Treatment				0.930	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.455	
Adjusted Rate per Patient per Year [95% CI]	0.182 [0.026, 1.258]	0.210 [0.034, 1.309]	0.343 [0.026, 4.540]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.864 [0.054, 13.92] 0.918
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.529 [0.018, 15.61] 0.713
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.632 [0.075, 35.44] 0.755

Produced: 18 December 2020, 5:17

Page 3 of 3

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12d1 Total Number Of Hospital Days Due To Asthma stratified by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	486	486	243		
Effect					
Treatment				0.886	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.406	
Adjusted Rate per Patient per Year [95% CI]	0.190 [0.053, 0.689]	0.124 [0.034, 0.448]	0.185 [0.031, 1.104]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.537 [0.243, 9.733] 0.648
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.031 [0.113, 9.433] 0.979
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.491 [0.166, 13.39] 0.721

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12e1 Total Number Of Hospital Days Due To Asthma stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	437	445	227		
Effect Treatment				0.935	
Adjusted Rate per Patient per Year [95% CI]	0.115 [0.028, 0.477]	0.161 [0.040, 0.653]	0.164 [0.023, 1.169]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.716 [0.097, 5.281] 0.743
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.701 [0.062, 7.924] 0.774
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.022 [0.092, 11.41] 0.986

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.12e1 Total Number Of Hospital Days Due To Asthma stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect Treatment				0.792	
Adjusted Rate per Patient per Year [95% CI]	0.466 [0.071, 3.044]	0.182 [0.025, 1.325]	0.251 [0.015, 4.313]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					2.557 [0.167, 39.25] 0.500
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.858 [0.062, 56.11] 0.722
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.377 [0.043, 44.16] 0.857

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.12f1 Total Number Of Hospital Days Due To Asthma stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400]					
Number of Patients Included in Model	298	275	146		
Effect					
Treatment				0.501	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.193	
Adjusted Rate per Patient per Year [95% CI]	0.051 [0.006, 0.412]	0.316 [0.046, 2.168]	0.250 [0.019, 3.277]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.160 [0.007, 3.629] 0.250
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.203 [0.006, 7.180] 0.381
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.790 [0.038, 16.58] 0.880

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12f1 Total Number Of Hospital Days Due To Asthma stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	270	290	139		
Effect					
Treatment				0.770	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.471	
Adjusted Rate per Patient per Year [95% CI]	0.232 [0.053, 1.013]	0.110 [0.026, 0.460]	0.185 [0.024, 1.424]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					2.117 [0.267, 16.81] 0.478
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.257 [0.100, 15.85] 0.860
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.684 [0.140, 20.24] 0.681

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12g1 Total Number Of Hospital Days Due To Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	128	137	74		
Effect					
Treatment				0.769	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.572	
Adjusted Rate per Patient per Year [95% CI]	0.162 [0.019, 1.364]	0.181 [0.023, 1.401]	0.547 [0.034, 8.688]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.898 [0.047, 17.17] 0.943
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.297 [0.009, 9.866] 0.497
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					3.026 [0.097, 94.72] 0.529

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12g1 Total Number Of Hospital Days Due To Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	441	428	211		
Effect					
Treatment				0.709	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.616	
Adjusted Rate per Patient per Year [95% CI]	0.169 [0.041, 0.691]	0.164 [0.042, 0.648]	0.064 [0.009, 0.486]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.028 [0.135, 7.851] 0.979
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.625 [0.206, 33.50] 0.458
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.392 [0.036, 4.294] 0.443

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12h1 Total Number Of Hospital Days Due To Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	284	134		
Effect					
Treatment				0.984	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.700	
Adjusted Rate per Patient per Year [95% CI]	0.267 [0.058, 1.238]	0.243 [0.057, 1.028]	0.305 [0.037, 2.527]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.100 [0.126, 9.600] 0.931
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.877 [0.059, 13.09] 0.924
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.254 [0.102, 15.45] 0.860

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12h1 Total Number Of Hospital Days Due To Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	296	281	151		
Effect					
Treatment				0.725	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.149	
Adjusted Rate per Patient per Year [95% CI]	0.071 [0.012, 0.415]	0.096 [0.015, 0.611]	0.020 [0.001, 0.443]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.736 [0.061, 8.902] 0.809
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					3.568 [0.086, 147.4] 0.503
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.206 [0.004, 9.954] 0.425

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12i1 Total Number Of Hospital Days Due To Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	317	315	159		
Effect					
Treatment				0.880	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.387	
Adjusted Rate per Patient per Year [95% CI]	0.147 [0.031, 0.691]	0.085 [0.018, 0.393]	0.095 [0.010, 0.868]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.736 [0.194, 15.55] 0.622
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.557 [0.098, 24.78] 0.754
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.115 [0.077, 16.22] 0.937

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.12i1 Total Number Of Hospital Days Due To Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	250	126		
Effect					
Treatment				0.916	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.707	
Adjusted Rate per Patient per Year [95% CI]	0.178 [0.033, 0.959]	0.272 [0.050, 1.470]	0.303 [0.029, 3.134]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.654 [0.058, 7.339] 0.731
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.588 [0.033, 10.42] 0.717
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.113 [0.062, 19.99] 0.942

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.13a Total Number Of Emergency Room Visits Due To Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Age Group			<0.001***
Age Group Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effects and log-time on study as an offset

Table 25.2.13b Total Number Of Emergency Room Visits Due To Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.431
Gender			<0.001***
Gender Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.13c Total Number Of Emergency Room Visits Due To Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.396
BMI Class			<0.001***
BMI Class Treatment Interaction			0.625

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.13d Total Number Of Emergency Room Visits Due To Asthma including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.307
Number of Asthma Exacerbations in Previous Year (1, >1)			0.486
Smoking Status			0.167
Smoking Status Treatment Interaction			0.404

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.13f Total Number Of Emergency Room Visits Due To Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Degree of reversibility at screening (delta FEV1)			<0.001***
Degree of reversibility at screening (delta FEV1) Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effects and log-time on study as an offset

Table 25.2.13g Total Number Of Emergency Room Visits Due To Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.209
Number of Asthma Exacerbations in Previous Year (1, >1)			0.317
Use of spacer			0.333
Use of spacer Treatment Interaction			0.424

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.13h Total Number Of Emergency Room Visits Due To Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.432
Relevant Concomitant Cardiovascular Disease			<0.001***
Relevant Concomitant Cardiovascular Disease Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effects and log-time on study as an offset

Table 25.2.13i Total Number Of Emergency Room Visits Due To Asthma including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Region			<0.001***
Region Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effects and log-time on study as an offset

Table 25.2.14a Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.948
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Age Group			0.292
Age Group Treatment Interaction			0.937

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14b Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.963
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Gender			0.173
Gender Treatment Interaction			0.476

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14c Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.874
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
BMI Class			0.201
BMI Class Treatment Interaction			0.562

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14d Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.453
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Smoking Status			0.003
Smoking Status Treatment Interaction			0.138

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14e Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.793
Number of Exacerbation in the Previous year			<0.001***
Number of Exacerbation in the Previous year Treatment Interaction			0.841

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment a covariate

Table 25.2.14f Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.840
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Degree of reversibility at screening (delta FEV1)			0.137
Degree of reversibility at screening (delta FEV1) Treatment Interaction			0.857

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14g Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.942
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Use of spacer			0.556
Use of spacer Treatment Interaction			0.555

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14h Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.889
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Relevant Concomitant Cardiovascular Disease			0.028
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.755

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14i Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.914
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Region			0.044
Region Treatment Interaction			0.657

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.14a1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group:<65 years old					
Number of Patients Included in Model	472	444	244		
Effect Treatment				0.380	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.003**	
Adjusted Rate per Patient per Year [95% CI]	0.500 [0.381, 0.656]	0.486 [0.368, 0.642]	0.661 [0.458, 0.954]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.028 [0.697, 1.517] 0.888
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.756 [0.478, 1.194] 0.230
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.361 [0.858, 2.158] 0.190

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14a1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	97	121	41		
Effect					
Treatment				0.188	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.176	
Adjusted Rate per Patient per Year [95% CI]	0.712 [0.441, 1.150]	0.458 [0.289, 0.724]	0.309 [0.130, 0.732]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.556 [0.801, 3.023] 0.191
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.306 [0.859, 6.190] 0.097
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.675 [0.254, 1.794] 0.431

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14b1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	242	101		
Effect Treatment				0.744	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.025*	
Adjusted Rate per Patient per Year [95% CI]	0.397 [0.258, 0.611]	0.454 [0.309, 0.669]	0.525 [0.292, 0.945]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.873 [0.489, 1.556] 0.645
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.755 [0.364, 1.566] 0.450
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.156 [0.572, 2.337] 0.686

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14b1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	357	323	184		
Effect Treatment				0.473	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.020*	
Adjusted Rate per Patient per Year [95% CI]	0.619 [0.465, 0.824]	0.499 [0.367, 0.678]	0.657 [0.441, 0.981]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.241 [0.816, 1.887] 0.313
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.942 [0.576, 1.539] 0.811
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.317 [0.795, 2.182] 0.285

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14c1 Total Number Of Unscheduled Contacts Due To Asthma stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.056	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.377	
Adjusted Rate per Patient per Year [95% CI]	0.365 [0.225, 0.594]	0.498 [0.326, 0.763]	0.941 [0.518, 1.709]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.733 [0.383, 1.405] 0.349
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.388 [0.179, 0.845] 0.017*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.887 [0.908, 3.921] 0.089

Produced: 18 December 2020, 5:17

Page 1 of 3

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14c1 Total Number Of Unscheduled Contacts Due To Asthma stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	216	200	110		
Effect					
Treatment				0.350	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.274	
Adjusted Rate per Patient per Year [95% CI]	0.568 [0.376, 0.857]	0.365 [0.233, 0.573]	0.418 [0.229, 0.760]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.555 [0.844, 2.864] 0.157
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.360 [0.658, 2.813] 0.407
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.143 [0.541, 2.416] 0.726

Produced: 18 December 2020, 5:17

Page 2 of 3

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14c1 Total Number Of Unscheduled Contacts Due To Asthma stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	203	202	102		
Effect Treatment				0.902	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Rate per Patient per Year [95% CI]	0.618 [0.429, 0.889]	0.554 [0.383, 0.801]	0.553 [0.326, 0.938]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.115 [0.664, 1.871] 0.680
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.117 [0.588, 2.122] 0.735
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.998 [0.524, 1.900] 0.995

Produced: 18 December 2020, 5:17

Page 3 of 3

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14d1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	486	486	243		
Effect Treatment				0.357	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Rate per Patient per Year [95% CI]	0.474 [0.367, 0.613]	0.466 [0.361, 0.601]	0.346 [0.236, 0.506]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.019 [0.710, 1.462] 0.920
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.373 [0.868, 2.172] 0.176
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.742 [0.469, 1.173] 0.201

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14d1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	79	42		
Effect Treatment				0.027*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.341	
Adjusted Rate per Patient per Year [95% CI]	0.881 [0.509, 1.525]	0.568 [0.315, 1.025]	2.074 [1.001, 4.299]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.552 [0.690, 3.493] 0.288
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.425 [0.171, 1.053] 0.065
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					3.653 [1.412, 9.448] 0.008**

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14e1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	437	445	227		
Effect Treatment				0.421	
Adjusted Rate per Patient per Year [95% CI]	0.483 [0.357, 0.653]	0.404 [0.298, 0.546]	0.563 [0.373, 0.848]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.196 [0.781, 1.833] 0.410
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.858 [0.516, 1.429] 0.557
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.394 [0.837, 2.320] 0.202

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.14e1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.945	
Adjusted Rate per Patient per Year [95% CI]	0.792 [0.542, 1.159]	0.866 [0.588, 1.275]	0.802 [0.455, 1.414]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.914 [0.532, 1.573] 0.746
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.987 [0.499, 1.953] 0.970
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.926 [0.466, 1.840] 0.827

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment as fixed effect and log-time on study as an offset

Table 25.2.14f1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400]					
Number of Patients Included in Model	298	275	146		
Effect					
Treatment				0.382	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.107	
Adjusted Rate per Patient per Year [95% CI]	0.651 [0.476, 0.890]	0.566 [0.408, 0.786]	0.834 [0.539, 1.293]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.150 [0.730, 1.811] 0.546
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.780 [0.455, 1.336] 0.366
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.474 [0.852, 2.552] 0.165

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14f1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	270	290	139		
Effect					
Treatment				0.943	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Rate per Patient per Year [95% CI]	0.401 [0.280, 0.576]	0.397 [0.281, 0.561]	0.362 [0.217, 0.601]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.012 [0.614, 1.666] 0.963
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.110 [0.596, 2.069] 0.742
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.911 [0.493, 1.685] 0.767

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14g1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	128	137	74		
Effect					
Treatment				0.839	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Rate per Patient per Year [95% CI]	0.530 [0.330, 0.851]	0.513 [0.324, 0.812]	0.638 [0.350, 1.163]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.032 [0.530, 2.012] 0.925
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.830 [0.386, 1.782] 0.632
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.244 [0.586, 2.645] 0.570

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14g1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	441	428	211		
Effect					
Treatment				0.416	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.322	
Adjusted Rate per Patient per Year [95% CI]	0.552 [0.419, 0.728]	0.441 [0.332, 0.585]	0.580 [0.391, 0.861]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.254 [0.843, 1.865] 0.265
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.952 [0.587, 1.544] 0.843
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.317 [0.810, 2.139] 0.267

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14h1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	284	134		
Effect					
Treatment				0.471	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.021*	
Adjusted Rate per Patient per Year [95% CI]	0.699 [0.505, 0.966]	0.585 [0.424, 0.807]	0.822 [0.521, 1.299]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.194 [0.757, 1.884] 0.446
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.849 [0.484, 1.490] 0.569
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.406 [0.802, 2.465] 0.235

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14h1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	296	281	151		
Effect					
Treatment				0.936	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.005**	
Adjusted Rate per Patient per Year [95% CI]	0.383 [0.271, 0.540]	0.368 [0.258, 0.523]	0.411 [0.254, 0.664]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.041 [0.636, 1.703] 0.874
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.931 [0.516, 1.680] 0.814
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.117 [0.616, 2.024] 0.715

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14i1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	317	315	159		
Effect					
Treatment				0.664	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.001**	
Adjusted Rate per Patient per Year [95% CI]	0.650 [0.483, 0.874]	0.539 [0.399, 0.729]	0.632 [0.416, 0.959]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.205 [0.790, 1.839] 0.387
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.029 [0.617, 1.716] 0.914
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.172 [0.700, 1.960] 0.547

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.14i1 Total Number Of Unscheduled Contacts Due To Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	250	126		
Effect					
Treatment				0.543	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.268	
Adjusted Rate per Patient per Year [95% CI]	0.384 [0.258, 0.570]	0.412 [0.278, 0.613]	0.557 [0.323, 0.962]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.930 [0.530, 1.631] 0.800
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.688 [0.351, 1.350] 0.277
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.351 [0.683, 2.671] 0.387

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.15a Statistical Analysis of Patients with Hospital Admission due to Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.671
Number of Asthma Exacerbations in the Previous year (1 >1)			0.387
Age Group			0.845
Age Group Treatment Interaction			0.455

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15b Statistical Analysis of Patients with Hospital Admission due to Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.955
Number of Asthma Exacerbations in the Previous year (1 >1)			0.471
Gender			0.208
Gender Treatment Interaction			0.885

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15c Statistical Analysis of Patients with Hospital Admission due to Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.723
Number of Asthma Exacerbations in the Previous year (1 >1)			0.363
BMI Class			0.612
BMI Class Treatment Interaction			0.660

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15d Statistical Analysis of Patients with Hospital Admission due to Asthma including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			1.000
Number of Asthma Exacerbations in the Previous year (1 >1)			0.392
Smoking Status			1.000
Smoking Status Treatment Interaction			1.000

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15e Statistical Analysis of Patients with Hospital Admission due to Asthma including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.711
Number of Exacerbation in the Previous year			0.626
Number of Exacerbation in the Previous year Treatment Interaction			0.602

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.15f Statistical Analysis of Patients with Hospital Admission due to Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.989
Number of Asthma Exacerbations in the Previous year (1 >1)			0.351
Degree of reversibility at screening (delta FEV1)			0.530
Degree of reversibility at screening (delta FEV1)			0.189
Treatment Interaction			

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15g Statistical Analysis of Patients with Hospital Admission due to Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.861
Number of Asthma Exacerbations in the Previous year (1 >1)			0.478
Use of spacer			0.365
Use of spacer Treatment Interaction			0.156

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15h Statistical Analysis of Patients with Hospital Admission due to Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.683
Number of Asthma Exacerbations in the Previous year (1 >1)			0.325
Relevant Concomitant Cardiovascular Disease			0.082
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.483

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15i Statistical Analysis of Patients with Hospital Admission due to Asthma including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.914
Number of Asthma Exacerbations in the Previous year (1 >1)			0.363
Region			0.782
Region Treatment Interaction			0.355

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15a1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Age Group:<65 years old					
Number of Patients Included in Model	472	444	244		
Effect					
Treatment				0.820	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.233	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.341 [0.506, 3.557] 0.555/ 1.331 [0.511, 3.466] 0.558/ 0.006 [-0.011, 0.023] 0.470
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.279 [0.397, 4.126] 0.680/ 1.273 [0.404, 4.016] 0.680/ 0.004 [-0.016, 0.024] 0.685
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.048 [0.304, 3.620] 0.940/ 1.046 [0.309, 3.535] 0.943/ 0.002 [-0.017, 0.021] 0.833

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15a1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Age Group: >= 65 years old					
Number of Patients Included in Model	97	121	41		
Effect					
Treatment				0.707	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.544	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.200 [0.074, 19.55] 0.898/ 1.209 [0.076, 19.09] 0.893/ -0.008 [-0.200, 0.183] 0.932
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.395 [0.024, 6.542] 0.517/ 0.407 [0.026, 6.357] 0.522/ -0.024 [-0.220, 0.172] 0.809
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					3.037 [0.185, 49.86] 0.436/ 2.968 [0.190, 46.25] 0.438/ 0.016 [-0.034, 0.065] 0.530

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15b1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Gender: Male					
Number of Patients Included in Model	212	242	101		
Effect					
Treatment				0.950	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.908	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.758 [0.125, 4.579] 0.762/ 0.760 [0.128, 4.508] 0.763/ -0.005 [-0.028, 0.019] 0.688
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.955 [0.086, 10.67] 0.970/ 0.956 [0.088, 10.42] 0.970/ -0.000 [-0.024, 0.023] 0.969
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.793 [0.081, 7.726] 0.842/ 0.796 [0.084, 7.564] 0.842/ -0.004 [-0.032, 0.023] 0.757

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15b1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Gender: Female					
Number of Patients Included in Model	357	323	184		
Effect					
Treatment				0.704	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.154	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.601 [0.530, 4.838] 0.404/ 1.585 [0.537, 4.679] 0.404/ 0.008 [-0.012, 0.029] 0.422
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.134 [0.344, 3.742] 0.836/ 1.134 [0.354, 3.628] 0.832/ 0.001 [-0.025, 0.027] 0.940
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.412 [0.374, 5.332] 0.611/ 1.398 [0.381, 5.135] 0.614/ 0.007 [-0.017, 0.031] 0.552

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15d1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Smoking Status: Non smoker					
Number of Patients Included in Model	486	486	243		
Effect					
Treatment				0.497	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.223	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.819 [0.667, 4.964] 0.243/ 1.800 [0.671, 4.828] 0.243/ 0.010 [-0.007, 0.026] 0.249
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.366 [0.430, 4.339] 0.597/ 1.358 [0.437, 4.219] 0.596/ 0.005 [-0.015, 0.025] 0.630
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.332 [0.372, 4.769] 0.659/ 1.325 [0.378, 4.648] 0.660/ 0.004 [-0.014, 0.023] 0.631

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15e1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	437	445	227		
Effect Treatment				0.759	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.433 [0.451, 4.548] 0.542/ 1.426 [0.456, 4.458] 0.542/ 0.005 [-0.011, 0.020] 0.540
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.908 [0.263, 3.133] 0.878/ 0.909 [0.269, 3.073] 0.878/ -0.002 [-0.022, 0.019] 0.880
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.578 [0.420, 5.936] 0.499/ 1.568 [0.425, 5.784] 0.499/ 0.006 [-0.013, 0.026] 0.526

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.15e1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect Treatment				0.872	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.219 [0.267, 5.560] 0.798/ 1.212 [0.277, 5.306] 0.798/ 0.005 [-0.035, 0.046] 0.797
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.781 [0.195, 16.29] 0.609/ 1.758 [0.201, 15.38] 0.610/ 0.013 [-0.031, 0.058] 0.565
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.684 [0.070, 6.724] 0.745/ 0.690 [0.073, 6.487] 0.745/ -0.008 [-0.051, 0.036] 0.727

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.15g1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Use of Spacer: Yes					
Number of Patients Included in Model	128	137	74		
Effect					
Treatment				0.554	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.268	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.724 [0.119, 4.416] 0.726/ 0.726 [0.124, 4.268] 0.723/ -0.002 [-0.032, 0.027] 0.874
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.383 [0.062, 2.358] 0.301/ 0.397 [0.068, 2.316] 0.305/ -0.025 [-0.073, 0.023] 0.308
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.888 [0.370, 9.636] 0.445/ 1.829 [0.380, 8.805] 0.451/ 0.023 [-0.026, 0.072] 0.367

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15g1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Use of Spacer: No					
Number of Patients Included in Model	441	428	211		
Effect					
Treatment				0.469	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.581	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.741 [0.578, 5.243] 0.324/ 1.726 [0.583, 5.114] 0.324/ 0.008 [-0.009, 0.025] 0.334
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.138 [0.457, 10.00] 0.334/ 2.117 [0.461, 9.723] 0.335/ 0.010 [-0.009, 0.029] 0.311
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.814 [0.157, 4.234] 0.807/ 0.816 [0.160, 4.169] 0.807/ -0.002 [-0.018, 0.015] 0.842

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15h1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	284	134		
Effect Treatment				0.699	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.974	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.470 [0.460, 4.693] 0.516/ 1.458 [0.468, 4.542] 0.516/ 0.008 [-0.016, 0.032] 0.521
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.856 [0.246, 2.982] 0.807/ 0.860 [0.256, 2.890] 0.807/ -0.004 [-0.040, 0.031] 0.806
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.717 [0.453, 6.498] 0.426/ 1.695 [0.463, 6.212] 0.426/ 0.012 [-0.021, 0.045] 0.462

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.15h1 Statistical Analysis of Patients with Hospital Admission due to Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	296	281	151		
Effect Treatment				0.813	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.025	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.279 [0.282, 5.806] 0.750/ 1.267 [0.288, 5.570] 0.754/ 0.004 [-0.011, 0.018] 0.610
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.031 [0.223, 18.46] 0.529/ 1.989 [0.226, 17.52] 0.536/ 0.009 [-0.043, 0.060] 0.742
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.630 [0.064, 6.149] 0.691/ 0.637 [0.067, 6.030] 0.694/ -0.005 [-0.056, 0.046] 0.854

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization due to asthma; non-response = Patient with no hospitalizations due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16a Statistical Analysis of Patients with Hospital Days due to Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.671
Number of Asthma Exacerbations in the Previous year (1 >1)			0.387
Age Group			0.845
Age Group Treatment Interaction			0.455

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16b Statistical Analysis of Patients with Hospital Days due to Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.955
Number of Asthma Exacerbations in the Previous year (1 >1)			0.471
Gender			0.208
Gender Treatment Interaction			0.885

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16c Statistical Analysis of Patients with Hospital Days due to Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.723
Number of Asthma Exacerbations in the Previous year (1 >1)			0.363
BMI Class			0.612
BMI Class Treatment Interaction			0.660

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16d Statistical Analysis of Patients with Hospital Days due to Asthma including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			1.000
Number of Asthma Exacerbations in the Previous year (1 >1)			0.392
Smoking Status			1.000
Smoking Status Treatment Interaction			1.000

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16e Statistical Analysis of Patients with Hospital Days due to Asthma
including Number of Exacerbation in the Previous year - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.711
Number of Exacerbation in the Previous year			0.626
Number of Exacerbation in the Previous year Treatment Interaction			0.602

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.16f Statistical Analysis of Patients with Hospital Days due to Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.989
Number of Asthma Exacerbations in the Previous year (1 >1)			0.351
Degree of reversibility at screening (delta FEV1)			0.530
Degree of reversibility at screening (delta FEV1)			0.189
Treatment Interaction			

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16g Statistical Analysis of Patients with Hospital Days due to Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.861
Number of Asthma Exacerbations in the Previous year (1 >1)			0.478
Use of spacer			0.365
Use of spacer Treatment Interaction			0.156

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16h Statistical Analysis of Patients with Hospital Days due to Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.683
Number of Asthma Exacerbations in the Previous year (1 >1)			0.325
Relevant Concomitant Cardiovascular Disease			0.082
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.483

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16i Statistical Analysis of Patients with Hospital Days due to Asthma including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.914
Number of Asthma Exacerbations in the Previous year (1 >1)			0.363
Region			0.782
Region Treatment Interaction			0.355

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16a1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Age Group:<65 years old					
Number of Patients Included in Model	472	444	244		
Effect					
Treatment				0.904	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.120	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.168 [0.456, 2.991] 0.746/ 1.160 [0.463, 2.911] 0.751/ 0.005 [-.012, 0.022] 0.560
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.274 [0.395, 4.111] 0.685/ 1.268 [0.402, 3.997] 0.686/ 0.004 [-.016, 0.024] 0.694
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.917 [0.273, 3.080] 0.889/ 0.915 [0.279, 3.006] 0.884/ 0.001 [-.018, 0.021] 0.910

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as
a covariate

Table 25.2.16a1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Age Group: >= 65 years old					
Number of Patients Included in Model	97	121	41		
Effect					
Treatment				0.820	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.760	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.609 [0.054, 6.841] 0.688/ 0.616 [0.057, 6.701] 0.691/ -.016 [-.207, 0.176] 0.873
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.407 [0.025, 6.709] 0.530/ 0.416 [0.027, 6.503] 0.532/ -.023 [-.218, 0.172] 0.815
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.494 [0.132, 16.94] 0.746/ 1.481 [0.138, 15.90] 0.746/ 0.008 [-.042, 0.058] 0.760

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as
a covariate

Table 25.2.16b1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Gender: Male					
Number of Patients Included in Model	212	242	101		
Effect					
Treatment				0.781	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.501	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.570 [0.103, 3.148] 0.519/ 0.572 [0.106, 3.091] 0.517/ -.005 [-.028, 0.019] 0.684
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.936 [0.084, 10.46] 0.957/ 0.937 [0.086, 10.21] 0.957/ -.000 [-.024, 0.023] 0.969
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.609 [0.067, 5.531] 0.660/ 0.611 [0.069, 5.402] 0.658/ -.004 [-.032, 0.023] 0.754

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16b1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Gender: Female					
Number of Patients Included in Model	357	323	184		
Effect					
Treatment				0.864	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.203	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.335 [0.469, 3.798] 0.589/ 1.327 [0.478, 3.686] 0.587/ 0.005 [-.016, 0.026] 0.648
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.138 [0.345, 3.753] 0.832/ 1.137 [0.355, 3.641] 0.829/ 0.001 [-.025, 0.027] 0.931
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.173 [0.326, 4.215] 0.807/ 1.167 [0.334, 4.077] 0.809/ 0.004 [-.021, 0.029] 0.765

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as
a covariate

Table 25.2.16d1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Smoking Status: Non smoker					
Number of Patients Included in Model	486	486	243		
Effect					
Treatment				0.497	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.223	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.819 [0.667, 4.964] 0.243/ 1.800 [0.671, 4.828] 0.243/ 0.010 [-.007, 0.026] 0.249
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.366 [0.430, 4.339] 0.597/ 1.358 [0.437, 4.219] 0.596/ 0.005 [-.015, 0.025] 0.630
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.332 [0.372, 4.769] 0.659/ 1.325 [0.378, 4.648] 0.660/ 0.004 [-.014, 0.023] 0.631

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as
a covariate

Table 25.2.16e1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	437	445	227		
Effect Treatment				0.908	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.191 [0.397, 3.573] 0.755/ 1.188 [0.402, 3.507] 0.755/ 0.003 [-.013, 0.018] 0.755
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.908 [0.263, 3.133] 0.878/ 0.909 [0.269, 3.073] 0.878/ -.002 [-.022, 0.019] 0.880
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.312 [0.367, 4.698] 0.676/ 1.307 [0.373, 4.584] 0.676/ 0.004 [-.016, 0.024] 0.688

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16e1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect Treatment				0.835	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.906 [0.222, 3.706] 0.891/ 0.909 [0.232, 3.555] 0.891/ -.003 [-.046, 0.040] 0.891
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.781 [0.195, 16.29] 0.609/ 1.758 [0.201, 15.38] 0.610/ 0.013 [-.031, 0.058] 0.565
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.509 [0.056, 4.657] 0.550/ 0.517 [0.059, 4.525] 0.551/ -.016 [-.063, 0.030] 0.497

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16g1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Use of Spacer: Yes					
Number of Patients Included in Model	128	137	74		
Effect					
Treatment				0.554	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.268	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.724 [0.119, 4.416] 0.726/ 0.726 [0.124, 4.268] 0.723/ -.002 [-.032, 0.027] 0.874
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.383 [0.062, 2.358] 0.301/ 0.397 [0.068, 2.316] 0.305/ -.025 [-.073, 0.023] 0.308
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.888 [0.370, 9.636] 0.445/ 1.829 [0.380, 8.805] 0.451/ 0.023 [-.026, 0.072] 0.367

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as
a covariate

Table 25.2.16g1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Use of Spacer: No					
Number of Patients Included in Model	441	428	211		
Effect					
Treatment				0.629	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.365	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.229 [0.453, 3.335] 0.686/ 1.224 [0.460, 3.260] 0.686/ 0.004 [-.014, 0.021] 0.685
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.116 [0.452, 9.901] 0.341/ 2.096 [0.456, 9.627] 0.341/ 0.009 [-.010, 0.028] 0.357
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.581 [0.120, 2.821] 0.500/ 0.584 [0.122, 2.786] 0.500/ -.005 [-.023, 0.013] 0.564

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as
a covariate

Table 25.2.16h1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	284	134		
Effect					
Treatment				0.858	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.887	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.224 [0.406, 3.692] 0.720/ 1.218 [0.414, 3.581] 0.720/ 0.005 [-.021, 0.030] 0.718
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.859 [0.247, 2.992] 0.812/ 0.862 [0.257, 2.898] 0.811/ -.004 [-.039, 0.032] 0.833
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.424 [0.395, 5.134] 0.589/ 1.412 [0.405, 4.921] 0.588/ 0.008 [-.025, 0.042] 0.622

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.16h1 Statistical Analysis of Patients with Hospital Days due to Asthma stratified by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	296	281	151		
Effect					
Treatment				0.789	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.010	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.953 [0.234, 3.886] 0.947/ 0.947 [0.241, 3.716] 0.938/ 0.004 [-.042, 0.049] 0.877
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.030 [0.223, 18.48] 0.530/ 1.982 [0.225, 17.43] 0.537/ 0.025 [-.057, 0.106] 0.556
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.470 [0.052, 4.278] 0.503/ 0.478 [0.054, 4.202] 0.506/ -.021 [-.101, 0.059] 0.606

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization day due to asthma; non-response = Patient with no hospitalization days due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17a Statistical Analysis of Patients with Emergency Room Visits due to Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in the Previous year (1 >1)			0.483
Age Group			<0.001***
Age Group Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17b Statistical Analysis of Patients with Emergency Room Visits due to Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in the Previous year (1 >1)			0.500
Gender			<0.001***
Gender Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17c Statistical Analysis of Patients with Emergency Room Visits due to Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in the Previous year (1 >1)			0.495
BMI Class			<0.001***
BMI Class Treatment Interaction			0.683

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17d Statistical Analysis of Patients with Emergency Room Visits due to Asthma including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.405
Number of Asthma Exacerbations in the Previous year (1 >1)			0.446
Smoking Status			0.038
Smoking Status Treatment Interaction			0.436

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17e Statistical Analysis of Patients with Emergency Room Visits due to Asthma including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.392
Number of Exacerbation in the Previous year			0.495
Number of Exacerbation in the Previous year Treatment Interaction			0.921

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.17f Statistical Analysis of Patients with Emergency Room Visits due to Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in the Previous year (1 >1)			0.429
Degree of reversibility at screening (delta FEV1)			<0.001***
Degree of reversibility at screening (delta FEV1)			<0.001***
Treatment Interaction			

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17g Statistical Analysis of Patients with Emergency Room Visits due to Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.449
Number of Asthma Exacerbations in the Previous year (1 >1)			0.658
Use of spacer			0.210
Use of spacer Treatment Interaction			0.497

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17h Statistical Analysis of Patients with Emergency Room Visits due to Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.606
Number of Asthma Exacerbations in the Previous year (1 >1)			0.440
Relevant Concomitant Cardiovascular Disease			<0.001***
Relevant Concomitant Cardiovascular Disease Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.17i Statistical Analysis of Patients with Emergency Room Visits due to Asthma
including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			<0.001***
Number of Asthma Exacerbations in the Previous year (1 >1)			0.439
Region			<0.001***
Region Treatment Interaction			<0.001***

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one hospitalization emergency room visit due to asthma; non-response = Patient with no emergency room visits due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18a Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.948
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Age Group			0.292
Age Group Treatment Interaction			0.937

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18b Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.963
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Gender			0.173
Gender Treatment Interaction			0.476

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18c Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.874
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
BMI Class			0.201
BMI Class Treatment Interaction			0.562

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18d Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.453
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Smoking Status			0.003
Smoking Status Treatment Interaction			0.138

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18e Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.793
Number of Exacerbation in the Previous year			<0.001***
Number of Exacerbation in the Previous year Treatment Interaction			0.841

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment a covariate

Table 25.2.18f Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.840
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Degree of reversibility at screening (delta FEV1)			0.137
Degree of reversibility at screening (delta FEV1)			0.857
Treatment Interaction			

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18g Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.942
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Use of spacer			0.556
Use of spacer Treatment Interaction			0.555

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18h Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.889
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Relevant Concomitant Cardiovascular Disease			0.028
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.755

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18i Statistical Analysis of Patients with Unscheduled Contacts due to Asthma including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.914
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Region			0.044
Region Treatment Interaction			0.657

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18a1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Age Group:<65 years old					
Number of Patients Included in Model	472	444	244		
Effect					
Treatment				0.585	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.866 [0.624, 1.202] 0.390/ 0.896 [0.693, 1.159] 0.404/ -0.023 [-0.074, 0.028] 0.372
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.036 [0.693, 1.551] 0.862/ 1.031 [0.746, 1.424] 0.853/ 0.004 [-0.054, 0.063] 0.887
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.836 [0.559, 1.249] 0.381/ 0.869 [0.632, 1.196] 0.390/ -0.027 [-0.087, 0.033] 0.372

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18a1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Age Group: >= 65 years old					
Number of Patients Included in Model	97	121	41		
Effect					
Treatment				0.864	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.011	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.849 [0.448, 1.609] 0.615/ 0.868 [0.541, 1.392] 0.556/ -0.022 [-0.132, 0.089] 0.700
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.988 [0.405, 2.408] 0.978/ 0.996 [0.508, 1.952] 0.991/ -0.003 [-0.151, 0.144] 0.964
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.859 [0.365, 2.024] 0.728/ 0.871 [0.458, 1.658] 0.674/ -0.018 [-0.163, 0.126] 0.803

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18b1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Gender: Male					
Number of Patients Included in Model	212	242	101		
Effect					
Treatment				0.310	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.006	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.685 [0.419, 1.119] 0.131/ 0.743 [0.498, 1.109] 0.146/ -0.057 [-0.125, 0.012] 0.106
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.859 [0.450, 1.640] 0.645/ 0.879 [0.515, 1.501] 0.637/ -0.018 [-0.104, 0.067] 0.673
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.797 [0.433, 1.469] 0.467/ 0.845 [0.515, 1.387] 0.505/ -0.038 [-0.126, 0.049] 0.392

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18b1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Gender: Female					
Number of Patients Included in Model	357	323	184		
Effect					
Treatment				0.716	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.945 [0.656, 1.362] 0.763/ 0.949 [0.720, 1.252] 0.711/ -0.006 [-0.067, 0.056] 0.854
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.141 [0.730, 1.783] 0.562/ 1.112 [0.785, 1.573] 0.550/ 0.019 [-0.051, 0.089] 0.597
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.828 [0.527, 1.302] 0.415/ 0.854 [0.601, 1.213] 0.378/ -0.025 [-0.096, 0.047] 0.500

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18c1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by BMI Class
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.580	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.274	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.756 [0.436, 1.308] 0.317/ 0.813 [0.526, 1.257] 0.352/ -0.054 [-0.144, 0.036] 0.239
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.943 [0.461, 1.929] 0.872/ 0.956 [0.537, 1.704] 0.880/ -0.011 [-0.120, 0.099] 0.850
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.801 [0.402, 1.596] 0.528/ 0.850 [0.490, 1.475] 0.564/ -0.043 [-0.154, 0.067] 0.443

Produced: 18 December 2020, 5:17

Page 1 of 3

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18c1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by BMI Class
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
BMI Class: [25-30)					
Number of Patients Included in Model	216	200	110		
Effect					
Treatment				0.613	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.015	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.026 [0.619, 1.701] 0.919/ 1.011 [0.671, 1.523] 0.960/ 0.008 [-0.065, 0.081] 0.831
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.362 [0.721, 2.571] 0.341/ 1.303 [0.768, 2.211] 0.326/ 0.034 [-0.047, 0.116] 0.410
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.754 [0.394, 1.443] 0.394/ 0.775 [0.450, 1.335] 0.359/ -0.026 [-0.109, 0.056] 0.529

Produced: 18 December 2020, 5:17

Page 2 of 3

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18c1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by BMI Class
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
BMI Class: >=30					
Number of Patients Included in Model	203	202	102		
Effect					
Treatment				0.676	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.809 [0.502, 1.304] 0.384/ 0.832 [0.590, 1.173] 0.294/ -0.024 [-0.102, 0.054] 0.549
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.857 [0.476, 1.544] 0.608/ 0.872 [0.566, 1.343] 0.535/ -0.016 [-0.111, 0.078] 0.734
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.944 [0.529, 1.684] 0.845/ 0.954 [0.629, 1.446] 0.823/ -0.008 [-0.105, 0.090] 0.879

Produced: 18 December 2020, 5:17

Page 3 of 3

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18d1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Smoking Status: Non smoker					
Number of Patients Included in Model	486	486	243		
Effect					
Treatment				0.268	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.855 [0.621, 1.177] 0.336/ 0.883 [0.687, 1.135] 0.332/ -0.023 [-0.072, 0.026] 0.354
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.188 [0.785, 1.799] 0.416/ 1.149 [0.819, 1.613] 0.421/ 0.024 [-0.033, 0.080] 0.411
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.720 [0.477, 1.084] 0.116/ 0.769 [0.551, 1.072] 0.121/ -0.047 [-0.104, 0.010] 0.109

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18d1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.447	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.021	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.846 [0.414, 1.728] 0.646/ 0.893 [0.535, 1.490] 0.664/ -0.032 [-0.164, 0.099] 0.629
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.586 [0.255, 1.342] 0.206/ 0.695 [0.397, 1.218] 0.204/ -0.106 [-0.273, 0.062] 0.215
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.445 [0.633, 3.299] 0.383/ 1.284 [0.745, 2.212] 0.368/ 0.073 [-0.098, 0.245] 0.401

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18e1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	437	445	227		
Effect Treatment				0.627	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.860 [0.608, 1.218] 0.396/ 0.883 [0.663, 1.177] 0.397/ -0.022 [-0.072, 0.028] 0.396
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.013 [0.657, 1.563] 0.954/ 1.011 [0.703, 1.453] 0.954/ 0.002 [-0.058, 0.061] 0.954
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.849 [0.555, 1.300] 0.452/ 0.874 [0.614, 1.244] 0.454/ -0.024 [-0.084, 0.037] 0.443

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.18e1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect Treatment				0.692	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.839 [0.492, 1.429] 0.518/ 0.886 [0.615, 1.277] 0.517/ -0.038 [-0.153, 0.077] 0.518
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.101 [0.554, 2.187] 0.784/ 1.071 [0.654, 1.754] 0.785/ 0.020 [-0.119, 0.158] 0.782
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.762 [0.382, 1.518] 0.440/ 0.828 [0.508, 1.348] 0.447/ -0.057 [-0.200, 0.085] 0.430

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.18f1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Degree of reversibility at screening
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	298	275	146		
Effect Treatment				0.329	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.764 [0.517, 1.129] 0.177/ 0.801 [0.598, 1.073] 0.137/ -0.040 [-0.109, 0.029] 0.254
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.008 [0.616, 1.648] 0.976/ 1.012 [0.690, 1.482] 0.953/ -0.001 [-0.080, 0.078] 0.984
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.759 [0.466, 1.235] 0.267/ 0.792 [0.546, 1.149] 0.220/ -0.039 [-0.122, 0.043] 0.351

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18f1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Degree of reversibility at screening
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	270	290	139		
Effect Treatment				0.917	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.959 [0.618, 1.489] 0.854/ 0.990 [0.696, 1.409] 0.956/ -0.015 [-0.076, 0.046] 0.631
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.077 [0.619, 1.872] 0.794/ 1.060 [0.677, 1.660] 0.800/ 0.011 [-0.063, 0.085] 0.775
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.891 [0.517, 1.537] 0.679/ 0.934 [0.601, 1.452] 0.762/ -0.026 [-0.099, 0.048] 0.490

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18g1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Use of Spacer: Yes					
Number of Patients Included in Model	128	137	74		
Effect					
Treatment				0.873	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.856 [0.466, 1.570] 0.615/ 0.817 [0.529, 1.264] 0.364/ 0.013 [-0.080, 0.105] 0.787
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.880 [0.429, 1.805] 0.727/ 0.883 [0.528, 1.477] 0.636/ -0.005 [-0.114, 0.103] 0.923
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.972 [0.484, 1.952] 0.937/ 0.926 [0.568, 1.508] 0.756/ 0.018 [-0.093, 0.129] 0.749

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18g1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Use of Spacer: No					
Number of Patients Included in Model	441	428	211		
Effect					
Treatment				0.440	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.007	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.867 [0.621, 1.209] 0.399/ 0.903 [0.694, 1.175] 0.447/ -0.028 [-0.081, 0.026] 0.309
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.129 [0.734, 1.739] 0.580/ 1.114 [0.783, 1.585] 0.547/ 0.013 [-0.049, 0.075] 0.679
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.767 [0.500, 1.178] 0.225/ 0.810 [0.572, 1.147] 0.236/ -0.041 [-0.104, 0.022] 0.206

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18h1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	284	134		
Effect Treatment				0.684	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.001	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.888 [0.599, 1.316] 0.554/ 0.910 [0.678, 1.221] 0.530/ -0.019 [-0.089, 0.050] 0.587
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.093 [0.658, 1.814] 0.732/ 1.084 [0.734, 1.602] 0.685/ 0.010 [-0.074, 0.093] 0.819
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.812 [0.493, 1.339] 0.416/ 0.840 [0.572, 1.231] 0.371/ -0.029 [-0.113, 0.055] 0.496

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18h1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	296	281	151		
Effect Treatment				0.684	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.831 [0.537, 1.284] 0.404/ 0.865 [0.610, 1.226] 0.416/ -0.026 [-0.086, 0.034] 0.393
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.967 [0.566, 1.652] 0.902/ 0.964 [0.624, 1.489] 0.868/ 0.000 [-0.070, 0.070] 0.997
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.859 [0.506, 1.459] 0.574/ 0.898 [0.587, 1.374] 0.620/ -0.026 [-0.098, 0.046] 0.477

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18i1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Region: Europe					
Number of Patients Included in Model	317	315	159		
Effect					
Treatment				0.555	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.872 [0.598, 1.273] 0.478/ 0.933 [0.710, 1.227] 0.620/ -0.031 [-0.094, 0.033] 0.344
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.120 [0.696, 1.802] 0.642/ 1.112 [0.779, 1.587] 0.559/ 0.010 [-0.064, 0.084] 0.792
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.779 [0.485, 1.250] 0.301/ 0.839 [0.591, 1.191] 0.327/ -0.041 [-0.116, 0.034] 0.289

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.18i1 Statistical Analysis of Patients with Unscheduled Contacts due to Asthma stratified by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Region: Rest of World					
Number of Patients Included in Model	252	250	126		
Effect					
Treatment				0.646	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.181	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.812 [0.510, 1.291] 0.378/ 0.833 [0.568, 1.222] 0.351/ -0.024 [-0.091, 0.042] 0.474
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.975 [0.542, 1.754] 0.932/ 0.975 [0.596, 1.597] 0.921/ -0.001 [-0.079, 0.076] 0.972
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.833 [0.468, 1.480] 0.533/ 0.854 [0.530, 1.377] 0.518/ -0.023 [-0.103, 0.058] 0.577

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one unscheduled contact due to asthma; non-response = Patient with no unscheduled contacts due to asthma

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.19a Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Age Group - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.330
Country			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.416
Age Group			0.889
Age Group Treatment Interaction			0.700

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19b Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Gender - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.405
Country			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.407
Gender			0.777
Gender Treatment Interaction			0.935

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19c Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including BMI Class - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.506
Country			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.437
BMI Class			0.730
BMI Class Treatment Interaction			0.446

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19d Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Smoking Status - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.151
Country			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.385
Smoking Status			0.589
Smoking Status Treatment Interaction			0.322

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19e Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Number of Exacerbation in the Previous year - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.242
Country			<0.001***
Number of Exacerbation in the Previous year			0.274
Number of Exacerbation in the Previous year Treatment Interaction			0.403

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19f Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Degree of reversibility at screening (delta FEV1) - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.583
Country			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.282
Degree of reversibility at screening (delta FEV1)			0.890
Degree of reversibility at screening (delta FEV1)			0.019*
Treatment Interaction			

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19g Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Use of spacer - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.377
Country			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.483
Use of spacer			0.703
Use of spacer Treatment Interaction			0.960

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19h Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Relevant Concomitant Cardiovascular Disease - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.336
Country			<0.001***
Number of Asthma Exacerbations in Previous Year (1, >1)			0.399
Relevant Concomitant Cardiovascular Disease			0.287
Relevant Concomitant Cardiovascular Disease Treatment			0.147
Interaction			

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19i Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations including Region - Interaction test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	119	51	
Effect			
Treatment			0.289
Number of Asthma Exacerbations in Previous Year (1, >1)			0.942
Region			0.447
Region Treatment Interaction			0.794

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19a1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group:<65 years old					
Number of Patients Included in Model	98	109	43		
Effect					
Treatment				0.625	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.579	
Adjusted Mean [95% CI]	7.568 [6.683, 8.453]	7.177 [6.338, 8.016]	6.813 [5.480, 8.146]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.391 [-0.833, 1.615] 0.530
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.755 [-0.845, 2.355] 0.353
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.364 [-1.940, 1.212] 0.649

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19a1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	21	33	8		
Effect					
Treatment				0.341	
Country				0.960	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.300	
Adjusted Mean [95% CI]	8.541 [6.803, 10.28]	7.322 [5.950, 8.693]	6.189 [3.259, 9.119]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					1.219 [-1.044, 3.482] 0.284
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.352 [-1.114, 5.818] 0.179
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.133 [-4.425, 2.160] 0.493

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19b1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	37	58	13		
Effect					
Treatment				0.694	
Country				0.177	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.172	
Adjusted Mean [95% CI]	8.032 [6.815, 9.248]	7.499 [6.529, 8.470]	7.134 [5.106, 9.162]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.532 [-1.052, 2.116] 0.507
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.897 [-1.456, 3.251] 0.451
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.365 [-2.629, 1.898] 0.749

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19b1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	82	84	38		
Effect					
Treatment				0.550	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.542	
Adjusted Mean [95% CI]	7.572 [6.562, 8.583]	7.019 [6.024, 8.014]	6.632 [5.144, 8.120]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.553 [-0.870, 1.976] 0.444
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.940 [-0.868, 2.749] 0.306
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.387 [-2.179, 1.405] 0.670

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19c1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	23	39	11		
Effect					
Treatment				0.758	
Country				0.173	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.684	
Adjusted Mean [95% CI]	6.746 [5.475, 8.018]	7.252 [6.296, 8.207]	6.665 [4.886, 8.445]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					-0.505 [-2.143, 1.132] 0.540
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.081 [-2.124, 2.286] 0.942
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.586 [-2.608, 1.435] 0.564

Produced: 18 December 2020, 5:17

Page 1 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19c1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	44	42	18		
Effect					
Treatment				0.791	
Country				0.010**	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.225	
Adjusted Mean [95% CI]	6.927 [5.908, 7.946]	7.434 [6.383, 8.486]	7.128 [5.516, 8.740]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					-0.508 [-1.981, 0.966] 0.496
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.201 [-2.109, 1.706] 0.834
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.306 [-2.251, 1.638] 0.755

Produced: 18 December 2020, 5:17

Page 2 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19c1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	52	61	22		
Effect					
Treatment				0.278	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.926	
Adjusted Mean [95% CI]	8.477 [7.063, 9.891]	7.329 [6.039, 8.619]	6.499 [4.326, 8.672]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					1.148 [-0.786, 3.081] 0.242
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.978 [-0.648, 4.604] 0.139
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.830 [-3.355, 1.694] 0.516

Produced: 18 December 2020, 5:17

Page 3 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19d1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	97	121	37		
Effect					
Treatment				0.818	
Country				0.086	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.039*	
Adjusted Mean [95% CI]	7.185 [6.540, 7.829]	7.016 [6.440, 7.592]	6.801 [5.760, 7.843]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.169 [-0.702, 1.039] 0.703
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.383 [-0.844, 1.611] 0.539
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.214 [-1.407, 0.978] 0.723

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19d1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	22	21	14		
Effect					
Treatment				0.724	
Country				0.096	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.757	
Adjusted Mean [95% CI]	9.409 [6.026, 12.79]	8.671 [5.240, 12.10]	7.207 [2.982, 11.43]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.738 [-4.183, 5.659] 0.764
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.202 [-3.312, 7.716] 0.426
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.464 [-6.943, 4.015] 0.593

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19e1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	74	95	32		
Effect					
Treatment				0.755	
Country				0.127	
Adjusted Mean [95% CI]	7.505 [6.608, 8.402]	7.664 [6.873, 8.456]	7.062 [5.698, 8.426]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					-0.159 [-1.364, 1.046] 0.794
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.443 [-1.191, 2.077] 0.593
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.602 [-2.185, 0.980] 0.454

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19e1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	45	47	19		
Effect					
Treatment				0.441	
Country				<0.001***	
Adjusted Mean [95% CI]	7.689 [6.200, 9.178]	6.754 [5.291, 8.217]	6.028 [3.745, 8.311]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.935 [-1.189, 3.060] 0.385
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.661 [-1.067, 4.389] 0.230
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.726 [-3.458, 2.006] 0.599

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19f1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	69	73	31		
Effect					
Treatment				0.029*	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.025*	
Adjusted Mean [95% CI]	8.371 [7.282, 9.459]	6.995 [5.934, 8.056]	5.831 [4.212, 7.451]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					1.375 [-0.164, 2.915] 0.079
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.539 [0.586, 4.493] 0.011*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.164 [-3.112, 0.784] 0.240

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19f1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	50	69	20		
Effect					
Treatment				0.240	
Country				0.104	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.647	
Adjusted Mean [95% CI]	6.606 [5.549, 7.663]	7.809 [6.908, 8.710]	7.466 [5.782, 9.149]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					-1.203 [-2.615, 0.209] 0.094
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.859 [-2.850, 1.131] 0.394
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.343 [-2.275, 1.588] 0.726

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19g1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	28	41	14		
Effect					
Treatment				0.361	
Country				0.265	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.092	
Adjusted Mean [95% CI]	7.599 [6.240, 8.959]	6.888 [5.816, 7.961]	5.887 [4.034, 7.740]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.711 [-1.068, 2.490] 0.428
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.713 [-0.664, 4.089] 0.155
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.002 [-3.110, 1.107] 0.347

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19g1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	91	101	37		
Effect					
Treatment				0.678	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.954	
Adjusted Mean [95% CI]	7.733 [6.787, 8.678]	7.414 [6.517, 8.311]	6.955 [5.471, 8.440]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.319 [-0.992, 1.631] 0.632
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.778 [-0.987, 2.543] 0.386
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.459 [-2.198, 1.280] 0.604

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19h1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	61	88	28		
Effect					
Treatment				0.121	
Country				<0.001***	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.798	
Adjusted Mean [95% CI]	8.310 [7.203, 9.418]	7.638 [6.719, 8.556]	6.212 [4.561, 7.864]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.672 [-0.773, 2.118] 0.360
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.098 [0.095, 4.100] 0.040*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.425 [-3.324, 0.474] 0.140

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19h1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	58	54	23		
Effect					
Treatment				0.752	
Country				0.012*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.112	
Adjusted Mean [95% CI]	7.122 [6.244, 7.999]	6.653 [5.746, 7.560]	7.050 [5.659, 8.440]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.469 [-0.808, 1.746] 0.469
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.072 [-1.583, 1.726] 0.932
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.397 [-1.266, 2.060] 0.637

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects

[2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19i1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	71	79	31		
Effect					
Treatment				0.513	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.883	
Adjusted Mean [95% CI]	8.021 [6.785, 9.256]	7.227 [6.051, 8.402]	6.873 [4.999, 8.746]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					0.794 [-0.915, 2.503] 0.360
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.148 [-1.092, 3.389] 0.313
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.354 [-2.573, 1.865] 0.753

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects
 [2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 25.2.19i1 Statistical Analysis of average number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	48	63	20		
Effect					
Treatment				0.401	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.053	
Adjusted Mean [95% CI]	7.117 [6.208, 8.026]	7.406 [6.611, 8.200]	6.293 [4.880, 7.706]		
CHF 5993 pMDI HS - CHF 1535 pMDI HS					-0.288 [-1.495, 0.919] 0.637
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.825 [-0.856, 2.505] 0.333
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.113 [-2.736, 0.510] 0.177

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on an ANOVA model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects
 [2] Analysis performed on patients with at least one exacerbation treated with Systemic Corticosteroids

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.496
Country			0.110
Number of Asthma Exacerbations in Previous Year (1, >1)			0.007**
Age Group			0.613
Age Group Treatment Interaction			0.913

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations

(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.249
Country			0.097
Number of Asthma Exacerbations in Previous Year (1, >1)			0.006**
Gender			0.336
Gender Treatment Interaction			0.881

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.467
Country			0.055
Number of Asthma Exacerbations in Previous Year (1, >1)			0.010**
BMI Class			0.216
BMI Class Treatment Interaction			0.509

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.737
Country			0.105
Number of Asthma Exacerbations in Previous Year (1, >1)			0.003**
Smoking Status			0.035*
Smoking Status Treatment Interaction			0.302

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.304
Country			0.087
Number of Exacerbation in the Previous year			0.017*
Number of Exacerbation in the Previous year Treatment Interaction			0.839

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.315
Country			0.134
Number of Asthma Exacerbations in Previous Year (1, >1)			0.005**
Degree of reversibility at screening (delta FEV1)			0.252
Degree of reversibility at screening (delta FEV1) Treatment Interaction			0.507

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.294
Country			0.094
Number of Asthma Exacerbations in Previous Year (1, >1)			0.010**
Use of spacer			0.787
Use of spacer Treatment Interaction			0.844

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations

(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.267
Country			0.075
Number of Asthma Exacerbations in Previous Year (1, >1)			0.004**
Relevant Concomitant Cardiovascular Disease			0.040*
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.718

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 14.2.2.1.2c Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.358
Number of Asthma Exacerbations in Previous Year (1, >1)			0.005**
Region Treatment Interaction			0.931

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the

previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20a1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group:<65 years old					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.171	
Country				0.041*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.003**	
Adjusted Rate per Patient per Year [95% CI]	1.939 [1.397, 2.689]	2.431 [1.738, 3.400]	1.412 [0.894, 2.230]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.797 [0.498, 1.278] 0.347
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.373 [0.782, 2.411] 0.270
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.581 [0.329, 1.025] 0.061

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20a1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.742	
Country				0.516	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.159	
Adjusted Rate per Patient per Year [95% CI]	2.260 [1.073, 4.763]	2.927 [1.539, 5.567]	1.776 [0.528, 5.974]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.772 [0.279, 2.139] 0.619
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.273 [0.285, 5.675] 0.752
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.607 [0.150, 2.448] 0.483

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20b1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.095	
Country				0.590	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.032*	
Adjusted Rate per Patient per Year [95% CI]	1.571 [0.916, 2.695]	2.878 [1.745, 4.745]	1.099 [0.494, 2.446]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.546 [0.259, 1.152] 0.112
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.430 [0.540, 3.784] 0.472
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.382 [0.146, 0.999] 0.050*

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20b1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.458	
Country				0.026*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.018*	
Adjusted Rate per Patient per Year [95% CI]	2.173 [1.520, 3.105]	2.468 [1.705, 3.573]	1.651 [0.991, 2.748]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.880 [0.526, 1.473] 0.627
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.316 [0.700, 2.476] 0.394
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.669 [0.356, 1.257] 0.212

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20c1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.041*	
Country				0.279	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.306	
Adjusted Rate per Patient per Year [95% CI]	0.894 [0.456, 1.753]	3.067 [1.636, 5.748]	1.244 [0.506, 3.061]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.292 [0.109, 0.778] 0.014*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.719 [0.234, 2.207] 0.564
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.406 [0.134, 1.232] 0.111

Produced: 18 December 2020, 5:17

Page 1 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20c1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.484	
Country				0.449	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.221	
Adjusted Rate per Patient per Year [95% CI]	1.702 [1.027, 2.822]	2.085 [1.239, 3.508]	1.202 [0.584, 2.475]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.817 [0.394, 1.691] 0.585
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.416 [0.582, 3.445] 0.443
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.577 [0.235, 1.413] 0.229

Produced: 18 December 2020, 5:17

Page 2 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20c1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.379	
Country				0.093	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.001**	
Adjusted Rate per Patient per Year [95% CI]	2.507 [1.601, 3.924]	2.974 [1.924, 4.596]	1.717 [0.902, 3.269]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.843 [0.448, 1.588] 0.597
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.460 [0.650, 3.276] 0.359
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.578 [0.267, 1.251] 0.164

Produced: 18 December 2020, 5:17

Page 3 of 3

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20d1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.012*	
Country				0.199	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.002**	
Adjusted Rate per Patient per Year [95% CI]	1.865 [1.343, 2.590]	2.585 [1.866, 3.582]	1.076 [0.671, 1.727]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.721 [0.453, 1.150] 0.170
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.733 [0.972, 3.089] 0.062
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.416 [0.234, 0.741] 0.003**

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20d1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.791	
Country				0.292	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.332	
Adjusted Rate per Patient per Year [95% CI]	2.452 [1.177, 5.107]	3.067 [1.507, 6.244]	3.848 [1.412, 10.49]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.799 [0.275, 2.328] 0.681
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.637 [0.173, 2.347] 0.498
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.255 [0.370, 4.250] 0.716

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20e1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	451	229		
Effect					
Treatment				0.120	
Country				0.162	
Adjusted Rate per Patient per Year [95% CI]	1.591 [1.084, 2.335]	2.320 [1.589, 3.386]	1.193 [0.696, 2.044]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.686 [0.399, 1.179] 0.173
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.334 [0.688, 2.587] 0.394
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.514 [0.265, 0.998] 0.049*

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 25.2.20e1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.294	
Country				0.211	
Adjusted Rate per Patient per Year [95% CI]	4.325 [2.709, 6.906]	4.362 [2.667, 7.135]	2.308 [1.135, 4.693]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.992 [0.489, 2.011] 0.981
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.874 [0.791, 4.441] 0.154
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.529 [0.221, 1.266] 0.153

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country as fixed effects, and log-time on study as an offset

Table 25.2.20f1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400]					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.162	
Country				0.019*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.074	
Adjusted Rate per Patient per Year [95% CI]	2.403 [1.630, 3.542]	2.639 [1.767, 3.939]	1.381 [0.789, 2.416]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.911 [0.517, 1.604] 0.746
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.740 [0.879, 3.445] 0.112
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.523 [0.263, 1.043] 0.066

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20f1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.231	
Country				0.051	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.008**	
Adjusted Rate per Patient per Year [95% CI]	1.539 [0.965, 2.454]	2.291 [1.465, 3.583]	1.186 [0.619, 2.274]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.672 [0.345, 1.307] 0.242
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.298 [0.577, 2.917] 0.529
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.518 [0.233, 1.151] 0.106

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20g1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.119	
Country				0.041*	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.002**	
Adjusted Rate per Patient per Year [95% CI]	1.417 [0.000, I]	1.281 [0.000, I]	0.515 [0.000, I]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.107 [0.455, 2.694] 0.823
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.753 [0.922, 8.223] 0.070
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.402 [0.157, 1.028] 0.057

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20g1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.241	
Country				0.137	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.055	
Adjusted Rate per Patient per Year [95% CI]	1.998 [1.408, 2.835]	2.476 [1.744, 3.516]	1.463 [0.882, 2.427]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.807 [0.489, 1.332] 0.401
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.366 [0.734, 2.542] 0.326
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.591 [0.319, 1.094] 0.094

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20h1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.131	
Country				0.209	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.022*	
Adjusted Rate per Patient per Year [95% CI]	2.379 [1.593, 3.552]	3.466 [2.357, 5.098]	1.758 [0.989, 3.125]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.686 [0.390, 1.207] 0.191
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.353 [0.665, 2.752] 0.404
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.507 [0.253, 1.015] 0.055

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20h1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.338	
Country				0.095	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.031*	
Adjusted Rate per Patient per Year [95% CI]	1.623 [1.032, 2.552]	1.732 [1.091, 2.749]	0.978 [0.515, 1.856]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.937 [0.484, 1.816] 0.848
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.660 [0.750, 3.676] 0.211
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.565 [0.255, 1.251] 0.159

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, country, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20i1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.255	
Number of Asthma Exacerbations in Previous Year (1, >1)				<0.001***	
Adjusted Rate per Patient per Year [95% CI]	2.204 [1.490, 3.260]	2.932 [1.983, 4.336]	1.671 [0.956, 2.919]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.752 [0.431, 1.311] 0.314
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.319 [0.669, 2.603] 0.425
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.570 [0.288, 1.129] 0.107

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.20i1 Statistical Analysis of total number of days with Systemic Corticosteroids due to asthma exacerbations stratified by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.396	
Number of Asthma Exacerbations in Previous Year (1, >1)				0.210	
Adjusted Rate per Patient per Year [95% CI]	2.048 [1.288, 3.256]	2.633 [1.654, 4.192]	1.503 [0.772, 2.927]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.778 [0.404, 1.498] 0.453
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.362 [0.604, 3.073] 0.456
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.571 [0.252, 1.293] 0.179

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Listing 16.2.6.2.6

Notes: [1] Analysis is based on a negative binomial model including treatment, number of asthma exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset

Table 25.2.21a Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.806
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Age Group			0.473
Age Group Treatment Interaction			0.541

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.21b Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.286
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Gender			0.121
Gender Treatment Interaction			0.565

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.21c Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.437
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
BMI Class			0.085
BMI Class Treatment Interaction			0.914

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.21d Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.817
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Smoking Status			0.001
Smoking Status Treatment Interaction			0.118

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days

of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year

as a covariate

Table 25.2.21e Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.492
Number of Exacerbation in the Previous year			<0.001***
Number of Exacerbation in the Previous year Treatment Interaction			0.696

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days

of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment as a covariate

Table 25.2.21f Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.322
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Degree of reversibility at screening (delta FEV1)			0.026
Degree of reversibility at screening (delta FEV1) Treatment Interaction			0.391

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days

of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year

as a covariate

Table 25.2.21g Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Use of spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.402
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Use of spacer			0.716
Use of spacer Treatment Interaction			0.888

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate

Table 25.2.21h Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Relevant Concomitant Cardiovascular Disease - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.370
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Relevant Concomitant Cardiovascular Disease			0.046
Relevant Concomitant Cardiovascular Disease Treatment Interaction			0.382

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days

of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year

as a covariate

Table 25.2.21i Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.392
Number of Asthma Exacerbations in the Previous year (1 >1)			<0.001***
Region			0.288
Region Treatment Interaction			0.807

Produced: 18 December 2020, 5:17

Page 1 of 1

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days

of treatment with Systemic Corticosteroids

[2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year

as a covariate

Table 25.2.21a1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Age Group:<65 years old					
Number of Patients Included in Model	473	448	246		
Effect Treatment				0.107	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.817 [0.597, 1.118] 0.206/ 0.860 [0.682, 1.086] 0.206/ -0.033 [-0.085, 0.020] 0.220
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.241 [0.830, 1.854] 0.293/ 1.177 [0.857, 1.617] 0.314/ 0.033 [-0.024, 0.091] 0.259
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.658 [0.442, 0.982] 0.040*/ 0.731 [0.535, 0.998] 0.048*/ -0.066 [-0.126, -0.006] 0.030*

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21a1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.528	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.005	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.701 [0.370, 1.327] 0.275/ 0.781 [0.489, 1.246] 0.299/ -0.064 [-0.173, 0.046] 0.254
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.913 [0.372, 2.240] 0.842/ 0.928 [0.471, 1.830] 0.830/ -0.012 [-0.158, 0.134] 0.869
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.768 [0.327, 1.801] 0.543/ 0.841 [0.446, 1.586] 0.592/ -0.051 [-0.197, 0.094] 0.489

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21b1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	244	103		
Effect Treatment				0.097	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.722 [0.453, 1.148] 0.169/ 0.799 [0.561, 1.137] 0.213/ -0.056 [-0.127, 0.016] 0.129
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.395 [0.713, 2.733] 0.331/ 1.293 [0.742, 2.256] 0.365/ 0.048 [-0.031, 0.127] 0.233
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.517 [0.271, 0.986] 0.045*/ 0.618 [0.363, 1.050] 0.075/ -0.104 [-0.184, -0.023] 0.011*

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21b1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.356	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.825 [0.579, 1.177] 0.289/ 0.862 [0.665, 1.118] 0.264/ -0.031 [-0.094, 0.032] 0.333
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.109 [0.715, 1.721] 0.644/ 1.082 [0.773, 1.514] 0.645/ 0.016 [-0.054, 0.087] 0.648
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.744 [0.479, 1.155] 0.188/ 0.797 [0.572, 1.111] 0.181/ -0.047 [-0.121, 0.026] 0.205

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 14.2.2.1.2e Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.186	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.020	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.634 [0.360, 1.115] 0.114/ 0.706 [0.451, 1.103] 0.126/ -0.073 [-0.160, 0.013] 0.098
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.067 [0.490, 2.322] 0.871/ 1.048 [0.547, 2.008] 0.888/ 0.014 [-0.085, 0.113] 0.786
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.594 [0.283, 1.247] 0.169/ 0.673 [0.366, 1.239] 0.204/ -0.087 [-0.190, 0.016] 0.098

Produced: 18 December 2020, 5:17

Page 1 of 3

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 14.2.2.1.2e Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect Treatment				0.608	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.003	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.936 [0.579, 1.511] 0.786/ 0.943 [0.648, 1.371] 0.758/ -0.008 [-0.084, 0.068] 0.837
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.270 [0.697, 2.313] 0.435/ 1.218 [0.752, 1.973] 0.422/ 0.030 [-0.055, 0.116] 0.484
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.737 [0.402, 1.351] 0.324/ 0.774 [0.475, 1.260] 0.303/ -0.038 [-0.125, 0.048] 0.384

Produced: 18 December 2020, 5:17

Page 2 of 3

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 14.2.2.1.2e Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	203	102		
Effect Treatment				0.334	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.785 [0.500, 1.231] 0.291/ 0.861 [0.640, 1.160] 0.325/ -0.045 [-0.128, 0.038] 0.285
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.170 [0.652, 2.099] 0.600/ 1.094 [0.716, 1.670] 0.679/ 0.032 [-0.063, 0.126] 0.510
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.671 [0.377, 1.194] 0.175/ 0.788 [0.522, 1.188] 0.255/ -0.077 [-0.174, 0.020] 0.120

Produced: 18 December 2020, 5:17

Page 3 of 3

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21d1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	491	245		
Effect Treatment				0.010	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.748 [0.551, 1.016] 0.064/ 0.801 [0.637, 1.007] 0.058/ -0.045 [-0.096, 0.006] 0.082
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.368 [0.902, 2.073] 0.140/ 1.265 [0.903, 1.771] 0.171/ 0.049 [-0.006, 0.104] 0.081
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.547 [0.364, 0.823] 0.004/ 0.633 [0.457, 0.877] 0.006/ -0.094 [-0.151, -0.037] 0.001

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21d1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.484	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.003	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.056 [0.517, 2.160] 0.880/ 1.098 [0.667, 1.809] 0.712/ -0.006 [-0.136, 0.124] 0.929
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.649 [0.284, 1.485] 0.306/ 0.790 [0.464, 1.345] 0.384/ -0.095 [-0.263, 0.073] 0.269
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.627 [0.704, 3.762] 0.255/ 1.391 [0.811, 2.387] 0.230/ 0.089 [-0.078, 0.256] 0.296

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21e1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p- value/ Risk Difference [95% CI] p- value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	451	229		
Effect Treatment				0.087	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.785 [0.561, 1.097] 0.156/ 0.822 [0.626, 1.078] 0.157/ -0.038 [-0.089, 0.014] 0.155
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.244 [0.798, 1.939] 0.336/ 1.201 [0.825, 1.750] 0.339/ 0.029 [-0.029, 0.087] 0.324
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.631 [0.409, 0.973] 0.037*/ 0.684 [0.476, 0.983] 0.040*/ -0.067 [-0.126, -0.008] 0.027*

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21e1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect Treatment				0.609	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.803 [0.481, 1.343] 0.404/ 0.870 [0.629, 1.205] 0.403/ -0.051 [-0.170, 0.068] 0.403
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.062 [0.551, 2.046] 0.858/ 1.041 [0.671, 1.613] 0.859/ 0.013 [-0.132, 0.159] 0.857
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.757 [0.391, 1.463] 0.407/ 0.836 [0.544, 1.287] 0.416/ -0.064 [-0.213, 0.085] 0.399

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21f1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.572	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.835 [0.568, 1.227] 0.359/ 0.865 [0.655, 1.141] 0.305/ -0.027 [-0.095, 0.041] 0.437
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.027 [0.634, 1.665] 0.913/ 1.030 [0.718, 1.478] 0.871/ 0.001 [-0.078, 0.081] 0.972
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.813 [0.502, 1.315] 0.399/ 0.839 [0.588, 1.198] 0.335/ -0.028 [-0.110, 0.053] 0.495

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21f1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Degree of reversibility at screening (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect Treatment				0.049	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.733 [0.484, 1.108] 0.140/ 0.804 [0.587, 1.103] 0.176/ -0.054 [-0.119, 0.011] 0.106
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.420 [0.803, 2.512] 0.228/ 1.300 [0.813, 2.079] 0.273/ 0.057 [-0.012, 0.127] 0.107
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.516 [0.297, 0.897] 0.019*/ 0.619 [0.395, 0.970] 0.036*/ -0.111 [-0.183, -0.040] 0.002

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21g1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	138	74		
Effect Treatment				0.131	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.649 [0.359, 1.174] 0.153/ 0.739 [0.506, 1.081] 0.119/ -0.056 [-0.152, 0.039] 0.249
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.287 [0.602, 2.750] 0.515/ 1.163 [0.678, 1.995] 0.584/ 0.038 [-0.058, 0.135] 0.434
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.504 [0.243, 1.047] 0.066/ 0.636 [0.386, 1.048] 0.076/ -0.095 [-0.198, 0.009] 0.073

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21g1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	433	213		
Effect Treatment				0.276	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.853 [0.618, 1.177] 0.333/ 0.893 [0.698, 1.143] 0.369/ -0.030 [-0.084, 0.025] 0.282
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.186 [0.778, 1.808] 0.427/ 1.147 [0.817, 1.609] 0.428/ 0.026 [-0.037, 0.089] 0.421
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.719 [0.474, 1.092] 0.122/ 0.779 [0.558, 1.087] 0.141/ -0.056 [-0.120, 0.008] 0.088

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21h1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect Treatment				0.032	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.630 [0.428, 0.925] 0.019*/ 0.714 [0.544, 0.939] 0.016*/ -0.084 [-0.155, -0.012] 0.022*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.011 [0.609, 1.677] 0.968/ 1.025 [0.698, 1.503] 0.901/ -0.003 [-0.086, 0.080] 0.939
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.623 [0.383, 1.015] 0.057/ 0.697 [0.487, 0.999] 0.049*/ -0.080 [-0.166, 0.005] 0.066

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21h1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	284	153		
Effect Treatment				0.464	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.056 [0.694, 1.607] 0.800/ 1.048 [0.759, 1.445] 0.777/ 0.006 [-0.055, 0.067] 0.857
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.397 [0.816, 2.391] 0.223/ 1.261 [0.819, 1.941] 0.292/ 0.058 [-0.010, 0.125] 0.094
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.756 [0.439, 1.302] 0.313/ 0.831 [0.536, 1.287] 0.407/ -0.052 [-0.120, 0.016] 0.131

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21i1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.286	
Number of Asthma Exacerbations in the Previous year (1 >1)				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.848 [0.583, 1.233] 0.387/ 0.905 [0.692, 1.184] 0.467/ -0.032 [-0.095, 0.032] 0.325
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.239 [0.764, 2.009] 0.385/ 1.161 [0.806, 1.673] 0.423/ 0.036 [-0.036, 0.109] 0.327
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.684 [0.424, 1.105] 0.120/ 0.780 [0.545, 1.116] 0.174/ -0.068 [-0.141, 0.005] 0.070

Produced: 18 December 2020, 5:17

Page 1 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

Table 25.2.21i1 Statistical Analysis of Patients treated with Systemic Corticosteroids due to asthma exacerbations stratified by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value/ Relative Risk [95% CI] p-value/ Risk Difference [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.140	
Number of Asthma Exacerbations in the Previous year (1 >1)				0.001	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.714 [0.466, 1.093] 0.121/ 0.766 [0.553, 1.060] 0.108/ -0.052 [-0.123, 0.019] 0.152
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.152 [0.653, 2.032] 0.626/ 1.124 [0.708, 1.784] 0.619/ 0.019 [-0.061, 0.098] 0.645
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.620 [0.357, 1.077] 0.089/ 0.681 [0.438, 1.060] 0.088/ -0.071 [-0.154, 0.012] 0.094

Produced: 18 December 2020, 5:17

Page 2 of 2

Source: Not available

- Notes: [1] Response = Patient with at least one day of treatment with Systemic Corticosteroids; non-response = Patient with no days of treatment with Systemic Corticosteroids
 [2] Analysis is based on a logistic model including treatment and number of Asthma exacerbations in the previous year as a covariate
 [3] Analysis conducted on the overall ITT population assigning total number of days=0 to both patients without exacerbations or to patients with exacerbation not treated with SCS

ADDITIONAL_TLF_BATCH2_EQ5D3L

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch2

Date of Production: 17/12/2020

Identification Code: Additional_TLF_batch2_EQ5D3L_CCD-05993AB2-02_20201217(Batch2)

Table 20.2.11a Statistical Analysis of EQ-5D-3L score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.178
Visit Period			<0.001***
Treatment*Visit Period			0.250
Baseline			<0.001***
Baseline*Visit Period			0.001**
Age Group			0.171
Age Group Treatment Interaction			0.783

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11a Statistical Analysis of EQ-5D-3L score including Age Group - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.199
Visit Period			<0.001***
Treatment*Visit Period			0.796
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Age Group			0.157
Age Group Treatment Interaction			0.271

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11b Statistical Analysis of EQ-5D-3L score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.034*
Visit Period			<0.001***
Treatment*Visit Period			0.250
Baseline			<0.001***
Baseline*Visit Period			0.001**
Gender			0.527
Gender Treatment Interaction			0.560

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11b Statistical Analysis of EQ-5D-3L score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.479
Visit Period			<0.001***
Treatment*Visit Period			0.796
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Gender			0.538
Gender Treatment Interaction			0.918

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11c Statistical Analysis of EQ-5D-3L score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.067
Visit Period			<0.001***
Treatment*Visit Period			0.253
Baseline			<0.001***
Baseline*Visit Period			0.001**
BMI Class			<0.001***
BMI Class Treatment Interaction			0.527

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11c Statistical Analysis of EQ-5D-3L score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.603
Visit Period			<0.001***
Treatment*Visit Period			0.797
Baseline			<0.001***
Baseline*Visit Period			<0.001***
BMI Class			0.585
BMI Class Treatment Interaction			0.548

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11d Statistical Analysis of EQ-5D-3L score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.022*
Visit Period			<0.001***
Treatment*Visit Period			0.252
Baseline			<0.001***
Baseline*Visit Period			0.001**
Smoking Status			0.021*
Smoking Status Treatment Interaction			0.236

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11d Statistical Analysis of EQ-5D-3L score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.085
Visit Period			<0.001***
Treatment*Visit Period			0.796
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Smoking Status			0.079
Smoking Status Treatment Interaction			0.078

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11e Statistical Analysis of EQ-5D-3L score including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.035*
Visit Period			<0.001***
Treatment*Visit Period			0.249
Baseline			<0.001***
Baseline*Visit Period			0.001**
Number of Exacerbation in the Previous year			0.374
Number of Exacerbation in the Previous year Treatment Interaction			0.475

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11e Statistical Analysis of EQ-5D-3L score including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.968
Visit Period			<0.001***
Treatment*Visit Period			0.797
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.062
Number of Exacerbation in the Previous year Treatment Interaction			0.300

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11f Statistical Analysis of EQ-5D-3L score including Degree of reversibility at screening (delta FEV1) - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.038*
Visit Period			<0.001***
Treatment*Visit Period			0.240
Baseline			<0.001***
Baseline*Visit Period			0.001**
Degree of reversibility at screening (delta FEV1)			0.005**
Degree of reversibility at screening (delta FEV1)			0.321
Treatment Interaction			

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11f Statistical Analysis of EQ-5D-3L score including Degree of reversibility at screening (delta FEV1) - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.489
Visit Period			<0.001***
Treatment*Visit Period			0.808
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.032*
Degree of reversibility at screening (delta FEV1)			0.649
Treatment Interaction			

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11g Statistical Analysis of EQ-5D-3L score including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.012*
Visit Period			<0.001***
Treatment*Visit Period			0.251
Baseline			<0.001***
Baseline*Visit Period			0.001**
Use of Spacer			0.476
Use of Spacer Treatment Interaction			0.135

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11g Statistical Analysis of EQ-5D-3L score including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.654
Visit Period			<0.001***
Treatment*Visit Period			0.796
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Use of Spacer			0.607
Use of Spacer Treatment Interaction			0.723

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11h Statistical Analysis of EQ-5D-3L score including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.030*
Visit Period			<0.001***
Treatment*Visit Period			0.254
Baseline			<0.001***
Baseline*Visit Period			0.001**
Relevant Concomitant Cardiovascular Diseases			<0.001***
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.448

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11h Statistical Analysis of EQ-5D-3L score including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.475
Visit Period			<0.001***
Treatment*Visit Period			0.798
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.003**
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.747

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11i Statistical Analysis of EQ-5D-3L score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
EQ5D Index			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.038*
Visit Period			<0.001***
Treatment*Visit Period			0.251
Baseline			<0.001***
Baseline*Visit Period			0.001**
Region			0.013*
Region Treatment Interaction			0.857

Produced: 17 December 2020 Page 1 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.11i Statistical Analysis of EQ-5D-3L score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
<hr/>			
VAS Score			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.499
Visit Period			<0.001***
Treatment*Visit Period			0.796
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Region			0.600
Region Treatment Interaction			0.936

Produced: 17 December 2020 Page 2 of 2

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: <65 years old					
EQ5D Index					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.084	
Visit Period				<0.001***	
Treatment*Visit Period				0.659	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	0.039	0.037	0.027		
[95% CI]	[0.028, 0.051]	[0.025, 0.049]	[0.010, 0.043]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.014, 0.019] 0.762
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.007, 0.033] 0.210
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.030, 0.010] 0.323

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.055	0.044	0.034		
[95% CI]	[0.042, 0.068]	[0.031, 0.058]	[0.017, 0.052]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.008, 0.029] 0.252
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.001, 0.043] 0.063
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.032, 0.012] 0.373
Visit 5 (Week 26)					
Adjusted Mean	0.062	0.050	0.052		
[95% CI]	[0.049, 0.075]	[0.036, 0.063]	[0.034, 0.070]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.006, 0.031] 0.197
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.012, 0.032] 0.376
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.020, 0.024] 0.845

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.068	0.057	0.043		
[95% CI]	[0.054, 0.081]	[0.043, 0.070]	[0.025, 0.062]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.008, 0.030] 0.263
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [0.001, 0.047] 0.040*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.037, 0.010] 0.267
Visit 7 (Week 52)					
Adjusted Mean	0.077	0.067	0.049		
[95% CI]	[0.064, 0.090]	[0.054, 0.081]	[0.031, 0.067]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.009, 0.028] 0.336
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.028 [0.005, 0.050] 0.015*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.041, 0.004] 0.105

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.005, 0.025] 0.182
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [0.002, 0.038] 0.030*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.028, 0.008] 0.298
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.056	0.046	0.043		
[95% CI]	[0.046, 0.067]	[0.035, 0.057]	[0.028, 0.058]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.064	0.054	0.044		
[95% CI]	[0.054, 0.074]	[0.043, 0.065]	[0.030, 0.059]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.953	
Visit Period				<0.001***	
Treatment*Visit Period				0.468	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.002	4.182	3.816		
[95% CI]	[3.087, 4.916]	[3.239, 5.125]	[2.543, 5.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.180 [-1.494, 1.133] 0.788
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.186 [-1.381, 1.753] 0.816
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.366 [-1.951, 1.219] 0.651

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.453	6.130	5.379		
[95% CI]	[4.378, 6.529]	[5.025, 7.235]	[3.883, 6.874]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.677 [-2.219, 0.865] 0.389
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.074 [-1.768, 1.917] 0.937
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.751 [-2.611, 1.109] 0.428
Visit 5 (Week 26)					
Adjusted Mean	7.346	6.722	6.853		
[95% CI]	[6.274, 8.418]	[5.620, 7.823]	[5.365, 8.342]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.624 [-0.913, 2.161] 0.426
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.492 [-1.342, 2.327] 0.599
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.132 [-1.721, 1.984] 0.889

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	7.949	7.787	8.449		
[95% CI]	[6.828, 9.070]	[6.639, 8.936]	[6.891, 10.008]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.162 [-1.443, 1.766] 0.843
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.500 [-2.420, 1.419] 0.609
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.662 [-1.275, 2.599] 0.503
Visit 7 (Week 52)					
Adjusted Mean	9.726	8.927	8.949		
[95% CI]	[8.618, 10.833]	[7.795, 10.058]	[7.406, 10.492]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.799 [-0.784, 2.382] 0.322
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.777 [-1.122, 2.676] 0.422
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.022 [-1.892, 1.936] 0.982

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.278 [-1.006, 1.562] 0.671
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.203 [-1.332, 1.738] 0.795
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.075 [-1.474, 1.624] 0.924
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.249	6.149	5.932		
[95% CI]	[5.350, 7.148]	[5.224, 7.074]	[4.682, 7.183]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.509	7.231	7.306		
[95% CI]	[6.613, 8.405]	[6.311, 8.151]	[6.060, 8.552]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
EQ5D Index					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.933	
Visit Period				0.095	
Treatment*Visit Period				0.600	
Baseline				<0.001***	
Baseline*Visit Period				0.180	
Visit 3 (Week 4)					
Adjusted Mean	0.040	0.042	0.024		
[95% CI]	[0.016, 0.065]	[0.020, 0.064]	[-0.014, 0.062]		
p-value	0.001**	<0.001***	0.213		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.034, 0.032] 0.939
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.029, 0.062] 0.478
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.062, 0.026] 0.431

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.041	0.027	0.005		
[95% CI]	[0.010, 0.072]	[-0.001, 0.055]	[-0.044, 0.054]		
p-value	0.010*	0.062	0.841		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.028, 0.056] 0.511
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.036 [-0.022, 0.094] 0.224
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.078, 0.035] 0.447
Visit 5 (Week 26)					
Adjusted Mean	0.040	0.058	0.061		
[95% CI]	[0.011, 0.069]	[0.031, 0.085]	[0.014, 0.108]		
p-value	0.008**	<0.001***	0.011*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.018 [-0.058, 0.022] 0.373
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.076, 0.035] 0.461
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.051, 0.057] 0.920

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.049	0.051	0.065		
[95% CI]	[0.020, 0.077]	[0.025, 0.077]	[0.019, 0.111]		
p-value	0.001**	<0.001***	0.006**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.042, 0.037] 0.899
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.016 [-0.070, 0.038] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.014 [-0.040, 0.067] 0.616
Visit 7 (Week 52)					
Adjusted Mean	0.053	0.054	0.038		
[95% CI]	[0.024, 0.083]	[0.027, 0.081]	[-0.009, 0.085]		
p-value	<0.001***	<0.001***	0.113		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.040, 0.040] 0.981
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.041, 0.071] 0.594
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.070, 0.039] 0.573

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.035, 0.028] 0.825
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.044, 0.044] 0.988
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.047, 0.039] 0.858
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.040	0.046	0.038		
[95% CI]	[0.016, 0.065]	[0.024, 0.068]	[-0.000, 0.076]		
p-value	0.001**	<0.001***	0.051		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.046	0.049	0.045		
[95% CI]	[0.022, 0.069]	[0.028, 0.070]	[0.008, 0.082]		
p-value	<0.001***	<0.001***	0.018*		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.369	
Visit Period				0.018*	
Treatment*Visit Period				0.868	
Baseline				<0.001***	
Baseline*Visit Period				0.135	
Visit 3 (Week 4)					
Adjusted Mean	5.396	3.631	2.494		
[95% CI]	[3.440, 7.352]	[1.881, 5.381]	[-0.511, 5.500]		
p-value	<0.001***	<0.001***	0.103		
CHF 5993 pMDI - CHF 1535 pMDI					1.765 [-0.861, 4.391] 0.187
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.902 [-0.684, 6.487] 0.112
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.137 [-4.614, 2.341] 0.520

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	6.892	4.917	4.653		
[95% CI]	[4.613, 9.170]	[2.861, 6.973]	[1.091, 8.216]		
p-value	<0.001***	<0.001***	0.011*		
CHF 5993 pMDI - CHF 1535 pMDI					1.975 [-1.097, 5.046] 0.207
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.238 [-1.989, 6.466] 0.298
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.264 [-4.377, 3.850] 0.900
Visit 5 (Week 26)					
Adjusted Mean	7.197	5.043	4.667		
[95% CI]	[4.689, 9.706]	[2.762, 7.323]	[0.686, 8.648]		
p-value	<0.001***	<0.001***	0.022*		
CHF 5993 pMDI - CHF 1535 pMDI					2.155 [-1.239, 5.548] 0.212
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.530 [-2.175, 7.235] 0.291
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.375 [-4.963, 4.212] 0.872

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	8.492	7.378	5.529		
[95% CI]	[6.154, 10.829]	[5.253, 9.504]	[1.819, 9.238]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					1.114 [-2.049, 4.276] 0.489
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.963 [-1.421, 7.348] 0.184
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.850 [-6.124, 2.425] 0.395
Visit 7 (Week 52)					
Adjusted Mean	8.152	7.810	7.501		
[95% CI]	[5.602, 10.702]	[5.487, 10.134]	[3.454, 11.547]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.342 [-3.111, 3.794] 0.846
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.651 [-4.132, 5.435] 0.789
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.310 [-4.976, 4.356] 0.896

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					1.398 [-1.363, 4.159] 0.320
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.197 [-1.616, 6.009] 0.258
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.799 [-4.511, 2.914] 0.672
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.826	4.787	4.329		
[95% CI]	[4.761, 8.891]	[2.922, 6.652]	[1.094, 7.563]		
p-value	<0.001***	<0.001***	0.009**		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.581	6.182	5.384		
[95% CI]	[5.535, 9.626]	[4.330, 8.034]	[2.166, 8.601]		
p-value	<0.001***	<0.001***	0.001**		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12a Statistical Analysis of EQ-5D-3L score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
EQ5D Index					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.254	
Visit Period				0.074	
Treatment*Visit Period				0.851	
Baseline				<0.001***	
Baseline*Visit Period				0.175	
Visit 3 (Week 4)					
Adjusted Mean	0.046	0.032	0.028		
[95% CI]	[0.029, 0.063]	[0.017, 0.048]	[0.004, 0.053]		
p-value	<0.001***	<0.001***	0.025*		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.009, 0.037] 0.244
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.012, 0.048] 0.236
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.034, 0.025] 0.777

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.046	0.038	0.014		
[95% CI]	[0.027, 0.064]	[0.020, 0.055]	[-0.013, 0.041]		
p-value	<0.001***	<0.001***	0.295		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.018, 0.034] 0.541
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.002, 0.064] 0.062
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.055, 0.009] 0.156
Visit 5 (Week 26)					
Adjusted Mean	0.045	0.047	0.029		
[95% CI]	[0.026, 0.064]	[0.029, 0.065]	[0.002, 0.057]		
p-value	<0.001***	<0.001***	0.036*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.028, 0.025] 0.902
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.018, 0.049] 0.353
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.050, 0.015] 0.296

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.051	0.052	0.037		
[95% CI]	[0.032, 0.071]	[0.034, 0.070]	[0.009, 0.065]		
p-value	<0.001***	<0.001***	0.009**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.028, 0.025] 0.936
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.020, 0.048] 0.415
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.048, 0.018] 0.370
Visit 7 (Week 52)					
Adjusted Mean	0.064	0.057	0.035		
[95% CI]	[0.045, 0.083]	[0.040, 0.075]	[0.007, 0.062]		
p-value	<0.001***	<0.001***	0.015*		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.019, 0.033] 0.606
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.030 [-0.004, 0.063] 0.083
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.056, 0.010] 0.174

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.018, 0.024] 0.770
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.006, 0.048] 0.126
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.044, 0.009] 0.183
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.046	0.042	0.025		
[95% CI]	[0.030, 0.062]	[0.027, 0.057]	[0.002, 0.048]		
p-value	<0.001***	<0.001***	0.037*		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.051	0.048	0.030		
[95% CI]	[0.036, 0.067]	[0.034, 0.063]	[0.008, 0.053]		
p-value	<0.001***	<0.001***	0.008**		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.351	
Visit Period				<0.001***	
Treatment*Visit Period				0.108	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.031	2.872	3.922		
[95% CI]	[2.711, 5.351]	[1.635, 4.109]	[2.003, 5.842]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.159 [-0.649, 2.967] 0.208
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.109 [-2.223, 2.441] 0.927
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.051 [-1.237, 3.339] 0.367

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	4.562	4.902	4.629		
[95% CI]	[3.034, 6.090]	[3.472, 6.332]	[2.423, 6.836]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.340 [-2.432, 1.752] 0.750
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.068 [-2.753, 2.618] 0.961
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.272 [-2.906, 2.361] 0.839
Visit 5 (Week 26)					
Adjusted Mean	6.383	4.653	5.458		
[95% CI]	[4.776, 7.990]	[3.142, 6.164]	[3.130, 7.785]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.730 [-0.474, 3.935] 0.124
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.925 [-1.905, 3.756] 0.521
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.805 [-1.975, 3.585] 0.570

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	7.092	5.437	6.800		
[95% CI]	[5.420, 8.765]	[3.872, 7.002]	[4.375, 9.226]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.656 [-0.634, 3.945] 0.156
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.292 [-2.656, 3.240] 0.846
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.364 [-1.528, 4.255] 0.355
Visit 7 (Week 52)					
Adjusted Mean	8.631	6.269	5.839		
[95% CI]	[6.914, 10.348]	[4.663, 7.874]	[3.344, 8.334]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.362 [0.012, 4.712] 0.049*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.792 [-0.239, 5.822] 0.071
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.430 [-3.402, 2.543] 0.777

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					1.494 [-0.407, 3.394] 0.123
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.970 [-1.475, 3.415] 0.436
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.524 [-1.875, 2.923] 0.668
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	5.461	4.455	4.967		
[95% CI]	[4.110, 6.812]	[3.188, 5.723]	[3.010, 6.924]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	6.632	5.138	5.662		
[95% CI]	[5.244, 8.019]	[3.838, 6.438]	[3.651, 7.673]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
EQ5D Index					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.328	
Visit Period				<0.001***	
Treatment*Visit Period				0.278	
Baseline				<0.001***	
Baseline*Visit Period				0.001**	
Visit 3 (Week 4)					
Adjusted Mean	0.036	0.041	0.026		
[95% CI]	[0.023, 0.050]	[0.027, 0.055]	[0.008, 0.045]		
p-value	<0.001***	<0.001***	0.006**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.024, 0.015] 0.639
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.013, 0.033] 0.391
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.038, 0.009] 0.218

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.057	0.042	0.040		
[95% CI]	[0.042, 0.073]	[0.026, 0.058]	[0.019, 0.062]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.016 [-0.007, 0.038] 0.165
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.009, 0.044] 0.203
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.028, 0.026] 0.917
Visit 5 (Week 26)					
Adjusted Mean	0.066	0.054	0.067		
[95% CI]	[0.051, 0.081]	[0.038, 0.069]	[0.046, 0.088]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.009, 0.034] 0.262
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.001 [-0.027, 0.024] 0.923
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.014 [-0.013, 0.040] 0.307

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.072	0.056	0.053		
[95% CI]	[0.057, 0.088]	[0.040, 0.073]	[0.031, 0.075]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.016 [-0.007, 0.039] 0.161
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.007, 0.047] 0.154
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.031, 0.024] 0.807
Visit 7 (Week 52)					
Adjusted Mean	0.078	0.068	0.056		
[95% CI]	[0.063, 0.093]	[0.052, 0.084]	[0.035, 0.078]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.012, 0.032] 0.397
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.005, 0.048] 0.108
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.039, 0.015] 0.376

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.006, 0.030] 0.182
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.008, 0.034] 0.210
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.023, 0.020] 0.899
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.059	0.048	0.053		
[95% CI]	[0.046, 0.071]	[0.035, 0.061]	[0.035, 0.070]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.067	0.055	0.053		
[95% CI]	[0.055, 0.079]	[0.042, 0.068]	[0.036, 0.071]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.802	
Visit Period				<0.001***	
Treatment*Visit Period				0.899	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.417	4.863	3.545		
[95% CI]	[3.352, 5.482]	[3.744, 5.983]	[2.062, 5.029]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.446 [-1.991, 1.099] 0.571
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.872 [-0.954, 2.698] 0.349
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.318 [-3.176, 0.540] 0.164

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	6.426	6.505	5.703		
[95% CI]	[5.166, 7.686]	[5.182, 7.828]	[3.935, 7.472]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.079 [-1.906, 1.748] 0.932
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.723 [-1.449, 2.894] 0.514
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.802 [-3.010, 1.407] 0.476
Visit 5 (Week 26)					
Adjusted Mean	7.921	7.530	7.280		
[95% CI]	[6.668, 9.175]	[6.216, 8.845]	[5.519, 9.041]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.391 [-1.425, 2.208] 0.673
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.641 [-1.521, 2.803] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.250 [-2.447, 1.948] 0.823

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	8.667	9.268	8.840		
[95% CI]	[7.403, 9.931]	[7.943, 10.592]	[7.066, 10.615]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.601 [-2.431, 1.230] 0.520
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.173 [-2.352, 2.005] 0.876
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.427 [-2.641, 1.787] 0.705
Visit 7 (Week 52)					
Adjusted Mean	10.002	10.466	10.428		
[95% CI]	[8.755, 11.249]	[9.162, 11.770]	[8.674, 12.182]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.464 [-2.268, 1.340] 0.614
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.426 [-2.578, 1.726] 0.698
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-2.224, 2.148] 0.973

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					-0.210 [-1.678, 1.258] 0.779
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.206 [-1.539, 1.950] 0.817
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.416 [-2.190, 1.358] 0.646
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.922	6.804	6.221		
[95% CI]	[5.878, 7.967]	[5.708, 7.901]	[4.757, 7.684]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	8.103	8.313	7.897		
[95% CI]	[7.090, 9.115]	[7.250, 9.375]	[6.476, 9.317]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12b Statistical Analysis of EQ-5D-3L score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: < 25					
EQ5D Index					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.335	
Visit Period				0.006**	
Treatment*Visit Period				0.725	
Baseline				<0.001***	
Baseline*Visit Period				0.065	
Visit 3 (Week 4)					
Adjusted Mean	0.061	0.038	0.051		
[95% CI]	[0.040, 0.081]	[0.018, 0.058]	[0.021, 0.081]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.023 [-0.006, 0.052] 0.118
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.027, 0.046] 0.607
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.013 [-0.022, 0.049] 0.460

Produced: 17 December 2020 Page 1 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.055	0.032	0.057		
[95% CI]	[0.028, 0.081]	[0.007, 0.058]	[0.019, 0.095]		
p-value	<0.001***	0.013*	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					0.023 [-0.014, 0.059] 0.227
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.048, 0.044] 0.932
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.021, 0.070] 0.290
Visit 5 (Week 26)					
Adjusted Mean	0.070	0.052	0.080		
[95% CI]	[0.046, 0.095]	[0.029, 0.075]	[0.045, 0.115]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.019 [-0.015, 0.052] 0.278
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.009 [-0.052, 0.033] 0.669
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.028 [-0.014, 0.070] 0.193

Produced: 17 December 2020 Page 2 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.064	0.066	0.080		
[95% CI]	[0.040, 0.087]	[0.044, 0.089]	[0.046, 0.114]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.003 [-0.035, 0.030] 0.862
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.017 [-0.058, 0.024] 0.426
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.014 [-0.027, 0.054] 0.503
Visit 7 (Week 52)					
Adjusted Mean	0.088	0.070	0.094		
[95% CI]	[0.065, 0.110]	[0.048, 0.091]	[0.060, 0.127]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.018 [-0.013, 0.049] 0.261
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.006 [-0.046, 0.034] 0.778
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.024 [-0.016, 0.063] 0.239

Produced: 17 December 2020 Page 3 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.013, 0.040] 0.318
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.042, 0.026] 0.646
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.021 [-0.012, 0.055] 0.206
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.064	0.044	0.068		
[95% CI]	[0.043, 0.085]	[0.024, 0.064]	[0.039, 0.098]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 4 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.069	0.056	0.077		
[95% CI]	[0.050, 0.089]	[0.037, 0.074]	[0.050, 0.105]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 5 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.899	
Visit Period				<0.001***	
Treatment*Visit Period				0.980	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	3.775	4.512	4.883		
[95% CI]	[2.122, 5.429]	[2.925, 6.098]	[2.510, 7.255]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.737 [-3.027, 1.554] 0.528
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.107 [-4.000, 1.786] 0.452
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.371 [-2.484, 3.226] 0.799

Produced: 17 December 2020 Page 6 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	6.538	5.640	6.527		
[95% CI]	[4.560, 8.516]	[3.753, 7.526]	[3.705, 9.349]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.898 [-1.834, 3.631] 0.518
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-3.436, 3.458] 0.995
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.887 [-2.508, 4.282] 0.608
Visit 5 (Week 26)					
Adjusted Mean	7.717	7.049	7.517		
[95% CI]	[5.692, 9.742]	[5.118, 8.979]	[4.607, 10.428]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.668 [-2.129, 3.466] 0.639
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.199 [-3.348, 3.746] 0.912
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.469 [-3.025, 3.963] 0.792

Produced: 17 December 2020 Page 7 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	8.429	8.463	9.153		
[95% CI]	[6.399, 10.459]	[6.539, 10.386]	[6.227, 12.078]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.034 [-2.830, 2.763] 0.981
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.724 [-4.286, 2.838] 0.690
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.690 [-2.812, 4.192] 0.699
Visit 7 (Week 52)					
Adjusted Mean	9.587	9.208	9.861		
[95% CI]	[7.592, 11.582]	[7.323, 11.092]	[6.953, 12.768]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.379 [-2.365, 3.124] 0.786
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.274 [-3.801, 3.254] 0.879
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.653 [-2.813, 4.119] 0.711

Produced: 17 December 2020 Page 8 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.340 [-1.905, 2.585] 0.766
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.288 [-3.135, 2.560] 0.843
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.628 [-2.176, 3.431] 0.660
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.748	6.225	6.807		
[95% CI]	[5.068, 8.428]	[4.621, 7.829]	[4.400, 9.214]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.856	7.516	8.143		
[95% CI]	[6.229, 9.482]	[5.968, 9.064]	[5.807, 10.479]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: [25-30)					
EQ5D Index					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.248	
Visit Period				0.001**	
Treatment*Visit Period				0.599	
Baseline				<0.001***	
Baseline*Visit Period				0.018*	
Visit 3 (Week 4)					
Adjusted Mean	0.038	0.039	0.019		
[95% CI]	[0.022, 0.055]	[0.022, 0.056]	[-0.003, 0.042]		
p-value	<0.001***	<0.001***	0.096		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.024, 0.023] 0.937
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.009, 0.047] 0.184
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.048, 0.009] 0.169

Produced: 17 December 2020 Page 11 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.056	0.045	0.023		
[95% CI]	[0.039, 0.074]	[0.027, 0.064]	[-0.002, 0.048]		
p-value	<0.001***	<0.001***	0.072		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.015, 0.036] 0.400
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.033 [0.003, 0.064] 0.034*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.053, 0.009] 0.158
Visit 5 (Week 26)					
Adjusted Mean	0.053	0.053	0.052		
[95% CI]	[0.035, 0.071]	[0.035, 0.072]	[0.027, 0.077]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.026, 0.025] 0.968
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.030, 0.032] 0.957
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.033, 0.030] 0.932

Produced: 17 December 2020 Page 12 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.065	0.059	0.048		
[95% CI]	[0.046, 0.083]	[0.039, 0.078]	[0.021, 0.075]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.021, 0.033] 0.676
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.016, 0.049] 0.322
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.044, 0.023] 0.526
Visit 7 (Week 52)					
Adjusted Mean	0.069	0.066	0.040		
[95% CI]	[0.051, 0.088]	[0.047, 0.085]	[0.014, 0.066]		
p-value	<0.001***	<0.001***	0.003**		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.023, 0.030] 0.810
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.030 [-0.002, 0.062] 0.067
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.059, 0.006] 0.108

Produced: 17 December 2020 Page 13 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.017, 0.025] 0.722
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.007, 0.043] 0.155
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.040, 0.011] 0.267
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.052	0.049	0.038		
[95% CI]	[0.037, 0.066]	[0.034, 0.064]	[0.017, 0.059]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 14 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.059	0.055	0.041		
[95% CI]	[0.045, 0.074]	[0.040, 0.070]	[0.021, 0.062]		
p-value	<0.001***	<0.001***	<0.001***		
VAS Score					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.966	
Visit Period				<0.001***	
Treatment*Visit Period				0.611	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	3.900	3.645	2.969		
[95% CI]	[2.580, 5.221]	[2.273, 5.017]	[1.117, 4.821]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					0.255 [-1.649, 2.160] 0.792
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.932 [-1.344, 3.208] 0.422
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.676 [-2.982, 1.630] 0.565

Produced: 17 December 2020 Page 15 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	4.486	4.912	4.432		
[95% CI]	[2.881, 6.091]	[3.244, 6.581]	[2.152, 6.713]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.426 [-2.741, 1.889] 0.718
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.054 [-2.736, 2.844] 0.970
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.480 [-3.306, 2.346] 0.739
Visit 5 (Week 26)					
Adjusted Mean	6.672	5.931	6.821		
[95% CI]	[5.113, 8.232]	[4.300, 7.562]	[4.597, 9.045]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.741 [-1.515, 2.998] 0.519
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.149 [-2.866, 2.568] 0.914
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.890 [-1.868, 3.648] 0.526

Produced: 17 December 2020 Page 16 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	6.891	7.421	7.577		
[95% CI]	[5.263, 8.520]	[5.721, 9.120]	[5.257, 9.897]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.529 [-2.883, 1.824] 0.659
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.686 [-3.522, 2.150] 0.635
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.157 [-2.719, 3.033] 0.915
Visit 7 (Week 52)					
Adjusted Mean	9.070	8.078	8.031		
[95% CI]	[7.411, 10.729]	[6.346, 9.810]	[5.660, 10.402]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.992 [-1.406, 3.390] 0.417
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.038 [-1.857, 3.933] 0.481
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-2.983, 2.890] 0.975

Produced: 17 December 2020 Page 17 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.240 [-1.684, 2.164] 0.806
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.095 [-2.221, 2.411] 0.936
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.145 [-2.203, 2.493] 0.903
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	5.573	5.266	5.493		
[95% CI]	[4.262, 6.884]	[3.900, 6.631]	[3.633, 7.353]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 18 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	6.735	6.495	6.640		
[95% CI]	[5.403, 8.067]	[5.107, 7.883]	[4.747, 8.533]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 19 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: >=30					
EQ5D Index					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.135	
Visit Period				0.017*	
Treatment*Visit Period				0.562	
Baseline				<0.001***	
Baseline*Visit Period				0.110	
Visit 3 (Week 4)					
Adjusted Mean	0.026	0.036	0.016		
[95% CI]	[0.007, 0.044]	[0.018, 0.054]	[-0.010, 0.042]		
p-value	0.006**	<0.001***	0.218		
CHF 5993 pMDI - CHF 1535 pMDI					-0.011 [-0.036, 0.015] 0.408
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.022, 0.041] 0.554
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.052, 0.011] 0.205

Produced: 17 December 2020 Page 21 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.047	0.042	0.020		
[95% CI]	[0.028, 0.067]	[0.023, 0.062]	[-0.007, 0.047]		
p-value	<0.001***	<0.001***	0.156		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.022, 0.032] 0.723
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.028 [-0.006, 0.061] 0.103
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.056, 0.011] 0.180
Visit 5 (Week 26)					
Adjusted Mean	0.054	0.049	0.037		
[95% CI]	[0.034, 0.074]	[0.028, 0.069]	[0.009, 0.065]		
p-value	<0.001***	<0.001***	0.010*		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.023, 0.034] 0.711
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.018, 0.052] 0.339
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.046, 0.023] 0.514

Produced: 17 December 2020 Page 22 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.064	0.043	0.022		
[95% CI]	[0.043, 0.086]	[0.021, 0.064]	[-0.008, 0.052]		
p-value	<0.001***	<0.001***	0.144		
CHF 5993 pMDI - CHF 1535 pMDI					0.021 [-0.009, 0.052] 0.168
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.042 [0.005, 0.079] 0.027*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.057, 0.017] 0.279
Visit 7 (Week 52)					
Adjusted Mean	0.065	0.058	0.026		
[95% CI]	[0.044, 0.086]	[0.037, 0.079]	[-0.003, 0.056]		
p-value	<0.001***	<0.001***	0.075		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.023, 0.036] 0.661
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [0.002, 0.074] 0.037*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.032 [-0.068, 0.004] 0.083

Produced: 17 December 2020 Page 23 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.015, 0.032] 0.464
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.030 [0.001, 0.058] 0.040*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.049, 0.007] 0.145
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.048	0.045	0.028		
[95% CI]	[0.031, 0.064]	[0.028, 0.062]	[0.005, 0.052]		
p-value	<0.001***	<0.001***	0.018*		

Produced: 17 December 2020 Page 24 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.056	0.047	0.026		
[95% CI]	[0.040, 0.072]	[0.031, 0.064]	[0.003, 0.049]		
p-value	<0.001***	<0.001***	0.025*		

Produced: 17 December 2020 Page 25 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.463	
Visit Period				<0.001***	
Treatment*Visit Period				0.468	
Baseline				<0.001***	
Baseline*Visit Period				0.002**	
Visit 3 (Week 4)					
Adjusted Mean	4.985	4.029	3.545		
[95% CI]	[3.586, 6.384]	[2.626, 5.432]	[1.571, 5.519]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.956 [-1.026, 2.937] 0.344
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.440 [-0.979, 3.859] 0.243
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.484 [-2.906, 1.938] 0.695

Produced: 17 December 2020 Page 26 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	6.409	6.946	5.386		
[95% CI]	[4.854, 7.965]	[5.386, 8.506]	[3.203, 7.570]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.537 [-2.740, 1.667] 0.632
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.023 [-1.658, 3.704] 0.454
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.560 [-4.244, 1.125] 0.254
Visit 5 (Week 26)					
Adjusted Mean	7.695	6.157	5.806		
[95% CI]	[6.050, 9.341]	[4.507, 7.807]	[3.500, 8.112]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.538 [-0.792, 3.868] 0.195
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.890 [-0.943, 4.723] 0.191
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.352 [-3.188, 2.485] 0.808

Produced: 17 December 2020 Page 27 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	9.025	7.252	7.972		
[95% CI]	[7.350, 10.699]	[5.576, 8.929]	[5.626, 10.318]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.773 [-0.597, 4.142] 0.142
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.053 [-1.829, 3.935] 0.473
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.720 [-2.164, 3.604] 0.624
Visit 7 (Week 52)					
Adjusted Mean	9.786	8.904	8.926		
[95% CI]	[8.086, 11.487]	[7.208, 10.600]	[6.556, 11.296]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.882 [-1.519, 3.284] 0.471
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.861 [-2.056, 3.778] 0.562
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.022 [-2.893, 2.936] 0.988

Produced: 17 December 2020 Page 28 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					1.086 [-0.855, 3.027] 0.272
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.259 [-1.104, 3.622] 0.296
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.173 [-2.538, 2.192] 0.886
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.883	6.073	5.329		
[95% CI]	[5.503, 8.262]	[4.690, 7.456]	[3.391, 7.266]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 29 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	8.129	7.044	6.870		
[95% CI]	[6.758, 9.501]	[5.670, 8.417]	[4.946, 8.795]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 30 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12c Statistical Analysis of EQ-5D-3L score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 34 of 30

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
EQ5D Index					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.364	
Visit Period				<0.001***	
Treatment*Visit Period				0.305	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	0.045	0.040	0.034		
[95% CI]	[0.033, 0.056]	[0.028, 0.051]	[0.018, 0.051]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.011, 0.021] 0.551
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.009, 0.030] 0.301
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.025, 0.014] 0.584

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.058	0.046	0.035		
[95% CI]	[0.045, 0.071]	[0.033, 0.059]	[0.017, 0.054]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.007, 0.030] 0.209
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [0.000, 0.046] 0.047*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.034, 0.011] 0.333
Visit 5 (Week 26)					
Adjusted Mean	0.059	0.056	0.064		
[95% CI]	[0.046, 0.071]	[0.044, 0.069]	[0.046, 0.082]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.015, 0.020] 0.787
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.027, 0.017] 0.648
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.014, 0.029] 0.498

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.065	0.062	0.052		
[95% CI]	[0.052, 0.079]	[0.049, 0.075]	[0.034, 0.071]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.015, 0.022] 0.728
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.010, 0.036] 0.257
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.033, 0.013] 0.395
Visit 7 (Week 52)					
Adjusted Mean	0.074	0.069	0.055		
[95% CI]	[0.062, 0.087]	[0.056, 0.082]	[0.036, 0.073]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.013, 0.024] 0.561
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.003, 0.042] 0.083
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.037, 0.008] 0.207

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.010, 0.020] 0.502
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.007, 0.029] 0.224
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.024, 0.012] 0.504
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.056	0.051	0.050		
[95% CI]	[0.046, 0.067]	[0.040, 0.061]	[0.035, 0.066]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.063	0.058	0.052		
[95% CI]	[0.053, 0.073]	[0.048, 0.068]	[0.037, 0.067]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.929	
Visit Period				<0.001***	
Treatment*Visit Period				0.888	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.173	4.398	4.156		
[95% CI]	[3.286, 5.060]	[3.511, 5.285]	[2.902, 5.411]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.225 [-1.479, 1.029] 0.725
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-1.520, 1.553] 0.983
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.242 [-1.779, 1.295] 0.758

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.848	5.930	5.581		
[95% CI]	[4.813, 6.883]	[4.895, 6.965]	[4.114, 7.049]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.082 [-1.546, 1.381] 0.912
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.267 [-1.530, 2.063] 0.771
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.349 [-2.145, 1.448] 0.703
Visit 5 (Week 26)					
Adjusted Mean	7.363	6.727	7.359		
[95% CI]	[6.304, 8.421]	[5.667, 7.787]	[5.859, 8.859]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.635 [-0.862, 2.133] 0.405
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-1.832, 1.840] 0.997
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.632 [-1.205, 2.468] 0.500

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	8.229	8.116	8.626		
[95% CI]	[7.148, 9.310]	[7.036, 9.195]	[7.094, 10.159]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.113 [-1.414, 1.640] 0.884
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.398 [-2.273, 1.478] 0.678
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.511 [-1.364, 2.386] 0.593
Visit 7 (Week 52)					
Adjusted Mean	9.718	9.087	9.484		
[95% CI]	[8.627, 10.809]	[7.999, 10.175]	[7.933, 11.035]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.631 [-0.909, 2.172] 0.422
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.234 [-1.662, 2.130] 0.809
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.397 [-1.498, 2.292] 0.681

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.317 [-0.915, 1.549] 0.613
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.010 [-1.521, 1.502] 0.990
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.327 [-1.185, 1.839] 0.671
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.406	6.124	6.319		
[95% CI]	[5.526, 7.286]	[5.243, 7.004]	[5.072, 7.566]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.661	7.344	7.671		
[95% CI]	[6.790, 8.532]	[6.473, 8.215]	[6.436, 8.906]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
EQ5D Index					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.096	
Visit Period				0.034*	
Treatment*Visit Period				0.320	
Baseline				<0.001***	
Baseline*Visit Period				0.043*	
Visit 3 (Week 4)					
Adjusted Mean	0.009	0.026	-0.021		
[95% CI]	[-0.018, 0.035]	[-0.001, 0.053]	[-0.058, 0.016]		
p-value	0.515	0.058	0.272		
CHF 5993 pMDI - CHF 1535 pMDI					-0.017 [-0.055, 0.020] 0.363
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.029 [-0.016, 0.075] 0.204
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.093, -0.001] 0.045*

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.020	0.008	0.001		
[95% CI]	[-0.008, 0.047]	[-0.019, 0.036]	[-0.037, 0.039]		
p-value	0.157	0.548	0.962		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.028, 0.050] 0.570
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.028, 0.066] 0.434
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.055, 0.040] 0.755
Visit 5 (Week 26)					
Adjusted Mean	0.053	0.023	-0.014		
[95% CI]	[0.021, 0.084]	[-0.010, 0.055]	[-0.060, 0.032]		
p-value	0.001**	0.173	0.545		
CHF 5993 pMDI - CHF 1535 pMDI					0.030 [-0.015, 0.075] 0.194
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.067 [0.011, 0.122] 0.019*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.037 [-0.092, 0.019] 0.199

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.055	0.015	0.010		
[95% CI]	[0.024, 0.087]	[-0.018, 0.047]	[-0.035, 0.056]		
p-value	<0.001***	0.375	0.662		
CHF 5993 pMDI - CHF 1535 pMDI					0.041 [-0.005, 0.086] 0.078
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.045 [-0.010, 0.101] 0.109
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.060, 0.051] 0.874
Visit 7 (Week 52)					
Adjusted Mean	0.060	0.037	0.006		
[95% CI]	[0.030, 0.091]	[0.007, 0.068]	[-0.037, 0.050]		
p-value	<0.001***	0.018*	0.777		
CHF 5993 pMDI - CHF 1535 pMDI					0.023 [-0.021, 0.066] 0.299
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.054 [0.001, 0.107] 0.045*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.084, 0.022] 0.250

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.025 [-0.010, 0.059] 0.160
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.048 [0.006, 0.090] 0.027*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.065, 0.019] 0.286
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.036	0.019	-0.010		
[95% CI]	[0.011, 0.060]	[-0.007, 0.044]	[-0.046, 0.025]		
p-value	0.005**	0.146	0.560		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.047	0.022	-0.001		
[95% CI]	[0.022, 0.071]	[-0.003, 0.047]	[-0.036, 0.033]		
p-value	<0.001***	0.081	0.952		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.266	
Visit Period				0.002**	
Treatment*Visit Period				0.390	
Baseline				<0.001***	
Baseline*Visit Period				0.021*	
Visit 3 (Week 4)					
Adjusted Mean	4.771	1.743	0.874		
[95% CI]	[2.480, 7.063]	[-0.607, 4.092]	[-2.348, 4.096]		
p-value	<0.001***	0.145	0.593		
CHF 5993 pMDI - CHF 1535 pMDI					3.029 [-0.253, 6.310] 0.070
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.897 [-0.057, 7.852] 0.053
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.869 [-4.857, 3.120] 0.668

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	4.944	5.227	3.792		
[95% CI]	[2.133, 7.756]	[2.369, 8.086]	[-0.161, 7.745]		
p-value	<0.001***	<0.001***	0.060		
CHF 5993 pMDI - CHF 1535 pMDI					-0.283 [-4.292, 3.726] 0.889
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.152 [-3.699, 6.003] 0.640
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.436 [-6.315, 3.444] 0.562
Visit 5 (Week 26)					
Adjusted Mean	7.152	3.861	2.001		
[95% CI]	[4.455, 9.848]	[1.101, 6.622]	[-1.860, 5.861]		
p-value	<0.001***	0.006**	0.308		
CHF 5993 pMDI - CHF 1535 pMDI					3.290 [-0.569, 7.149] 0.094
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					5.151 [0.441, 9.861] 0.032*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.861 [-6.609, 2.888] 0.441

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	6.914	4.745	5.062		
[95% CI]	[4.094, 9.734]	[1.875, 7.615]	[1.058, 9.067]		
p-value	<0.001***	0.001**	0.013*		
CHF 5993 pMDI - CHF 1535 pMDI					2.169 [-1.854, 6.193] 0.289
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.852 [-3.046, 6.750] 0.457
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.317 [-4.611, 5.246] 0.899
Visit 7 (Week 52)					
Adjusted Mean	7.734	6.142	4.781		
[95% CI]	[4.957, 10.512]	[3.323, 8.961]	[0.843, 8.719]		
p-value	<0.001***	<0.001***	0.018*		
CHF 5993 pMDI - CHF 1535 pMDI					1.592 [-2.365, 5.550] 0.428
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					2.954 [-1.866, 7.773] 0.228
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.361 [-6.206, 3.484] 0.580

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					2.027 [-1.377, 5.431] 0.242
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					3.044 [-1.087, 7.175] 0.148
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.017 [-5.177, 3.143] 0.630
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.106	3.956	2.378		
[95% CI]	[3.763, 8.449]	[1.562, 6.349]	[-0.939, 5.696]		
p-value	<0.001***	0.001**	0.159		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	6.700	4.673	3.655		
[95% CI]	[4.316, 9.083]	[2.242, 7.104]	[0.282, 7.029]		
p-value	<0.001***	<0.001***	0.034*		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12d Statistical Analysis of EQ-5D-3L score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
EQ5D Index					
Number of Patients Included in Model	439	451	229		
Effect					
Treatment				0.204	
Visit Period				<0.001***	
Treatment*Visit Period				0.097	
Baseline				<0.001***	
Baseline*Visit Period				0.003**	
Visit 3 (Week 4)					
Adjusted Mean	0.041	0.041	0.034		
[95% CI]	[0.029, 0.053]	[0.029, 0.053]	[0.017, 0.050]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.017, 0.017] 0.976
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.013, 0.028] 0.478
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.008 [-0.028, 0.013] 0.462

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.054	0.040	0.035		
[95% CI]	[0.040, 0.068]	[0.026, 0.053]	[0.016, 0.054]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.005, 0.034] 0.145
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.005, 0.042] 0.119
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.028, 0.019] 0.716
Visit 5 (Week 26)					
Adjusted Mean	0.057	0.050	0.059		
[95% CI]	[0.044, 0.070]	[0.037, 0.063]	[0.040, 0.077]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.012, 0.025] 0.486
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.002 [-0.025, 0.021] 0.864
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.009 [-0.014, 0.031] 0.457

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.066	0.053	0.046		
[95% CI]	[0.052, 0.080]	[0.039, 0.067]	[0.026, 0.065]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.006, 0.033] 0.183
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.004, 0.045] 0.097
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.031, 0.017] 0.567
Visit 7 (Week 52)					
Adjusted Mean	0.073	0.059	0.040		
[95% CI]	[0.059, 0.087]	[0.046, 0.073]	[0.021, 0.059]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.006, 0.033] 0.162
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.033 [0.009, 0.056] 0.007**
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.042, 0.005] 0.115

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.005, 0.026] 0.175
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.016 [-0.003, 0.035] 0.099
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.024, 0.014] 0.592
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.054	0.046	0.048		
[95% CI]	[0.042, 0.065]	[0.034, 0.057]	[0.032, 0.063]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.061	0.051	0.045		
[95% CI]	[0.050, 0.072]	[0.040, 0.062]	[0.030, 0.061]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	439	451	229		
Effect					
Treatment				0.483	
Visit Period				<0.001***	
Treatment*Visit Period				0.777	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.078	3.870	3.292		
[95% CI]	[3.140, 5.015]	[2.941, 4.800]	[1.990, 4.595]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.207 [-1.113, 1.528] 0.758
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.785 [-0.820, 2.390] 0.337
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.578 [-2.179, 1.023] 0.479

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.481	5.635	5.105		
[95% CI]	[4.386, 6.575]	[4.551, 6.720]	[3.581, 6.629]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.155 [-1.696, 1.386] 0.844
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.375 [-1.501, 2.252] 0.695
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.530 [-2.402, 1.341] 0.578
Visit 5 (Week 26)					
Adjusted Mean	7.239	6.117	6.072		
[95% CI]	[6.106, 8.373]	[4.992, 7.242]	[4.490, 7.655]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.123 [-0.474, 2.720] 0.168
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.167 [-0.780, 3.114] 0.240
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-1.987, 1.898] 0.964

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	7.926	7.330	7.261		
[95% CI]	[6.752, 9.100]	[6.168, 8.492]	[5.622, 8.900]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.596 [-1.056, 2.248] 0.479
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.665 [-1.352, 2.682] 0.518
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.069 [-2.079, 1.941] 0.946
Visit 7 (Week 52)					
Adjusted Mean	9.121	8.212	7.641		
[95% CI]	[7.951, 10.292]	[7.055, 9.370]	[6.006, 9.277]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.909 [-0.737, 2.555] 0.279
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.480 [-0.532, 3.491] 0.149
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.571 [-2.575, 1.433] 0.576

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.665 [-0.677, 2.006] 0.331
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.953 [-0.683, 2.588] 0.253
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.288 [-1.919, 1.343] 0.729
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.212	5.623	5.347		
[95% CI]	[5.266, 7.157]	[4.685, 6.561]	[4.030, 6.664]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.345	6.680	6.392		
[95% CI]	[6.391, 8.298]	[5.736, 7.624]	[5.063, 7.720]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1 EQ5D Index					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.370	
Visit Period				<0.001***	
Treatment*Visit Period				0.693	
Baseline				<0.001***	
Baseline*Visit Period				0.002**	
Visit 3 (Week 4)					
Adjusted Mean	0.035	0.025	-0.002		
[95% CI]	[0.014, 0.057]	[0.002, 0.048]	[-0.034, 0.031]		
p-value	0.001**	0.031*	0.922		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.021, 0.042] 0.519
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.037 [-0.002, 0.076] 0.064
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.067, 0.013] 0.188

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and

baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.048	0.044	0.011		
[95% CI]	[0.025, 0.072]	[0.020, 0.068]	[-0.024, 0.046]		
p-value	<0.001***	<0.001***	0.533		
CHF 5993 pMDI - CHF 1535 pMDI					0.004 [-0.029, 0.038] 0.803
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.037 [-0.005, 0.079] 0.085
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.076, 0.010] 0.132
Visit 5 (Week 26)					
Adjusted Mean	0.062	0.056	0.031		
[95% CI]	[0.036, 0.087]	[0.030, 0.082]	[-0.007, 0.069]		
p-value	<0.001***	<0.001***	0.109		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.031, 0.042] 0.756
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.015, 0.076] 0.186
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.025 [-0.071, 0.021] 0.290

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.059	0.065	0.049		
[95% CI]	[0.035, 0.084]	[0.039, 0.090]	[0.012, 0.086]		
p-value	<0.001***	<0.001***	0.010*		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.041, 0.030] 0.771
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.011 [-0.034, 0.055] 0.642
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.061, 0.029] 0.492
Visit 7 (Week 52)					
Adjusted Mean	0.072	0.084	0.080		
[95% CI]	[0.048, 0.095]	[0.059, 0.108]	[0.044, 0.116]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.012 [-0.046, 0.022] 0.490
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.051, 0.035] 0.713
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.048, 0.040] 0.861

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					-0.001 [-0.028, 0.026] 0.931
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.016, 0.052] 0.305
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.054, 0.016] 0.280
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.054	0.048	0.020		
[95% CI]	[0.033, 0.074]	[0.026, 0.069]	[-0.010, 0.050]		
p-value	<0.001***	<0.001***	0.199		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.059	0.060	0.041		
[95% CI]	[0.040, 0.078]	[0.041, 0.080]	[0.013, 0.070]		
p-value	<0.001***	<0.001***	0.004**		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.601	
Visit Period				<0.001***	
Treatment*Visit Period				0.793	
Baseline				<0.001***	
Baseline*Visit Period				0.002**	
Visit 3 (Week 4)					
Adjusted Mean	4.880	4.627	5.086		
[95% CI]	[3.103, 6.658]	[2.763, 6.491]	[2.404, 7.767]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.253 [-2.323, 2.829] 0.847
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.206 [-3.423, 3.012] 0.900
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.459 [-2.807, 3.725] 0.782

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	6.531	6.657	6.023		
[95% CI]	[4.413, 8.648]	[4.440, 8.873]	[2.823, 9.223]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.126 [-3.192, 2.940] 0.936
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.508 [-3.329, 4.345] 0.795
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.634 [-4.527, 3.259] 0.749
Visit 5 (Week 26)					
Adjusted Mean	7.671	7.112	8.735		
[95% CI]	[5.647, 9.696]	[4.993, 9.231]	[5.684, 11.786]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.560 [-2.371, 3.491] 0.707
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.063 [-4.725, 2.598] 0.568
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.623 [-2.092, 5.338] 0.391

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	8.511	8.893	11.338		
[95% CI]	[6.556, 10.466]	[6.851, 10.934]	[8.398, 14.279]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.382 [-3.208, 2.445] 0.791
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.827 [-6.358, 0.704] 0.116
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.446 [-1.134, 6.026] 0.180
Visit 7 (Week 52)					
Adjusted Mean	10.572	10.450	13.307		
[95% CI]	[8.546, 12.597]	[8.344, 12.555]	[10.228, 16.385]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.122 [-2.799, 3.044] 0.934
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-2.735 [-6.420, 0.950] 0.145
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.857 [-0.873, 6.587] 0.133

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.076 [-2.237, 2.389] 0.948
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.616 [-4.509, 1.277] 0.272
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.693 [-1.242, 4.627] 0.257
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.891	6.589	7.339		
[95% CI]	[5.188, 8.594]	[4.805, 8.373]	[4.769, 9.909]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	8.177	8.100	9.793		
[95% CI]	[6.578, 9.775]	[6.428, 9.772]	[7.381, 12.204]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12e Statistical Analysis of EQ-5D-3L score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL EQ5D Index					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.086	
Visit Period				<0.001***	
Treatment*Visit Period				0.676	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	0.036	0.034	0.014		
[95% CI]	[0.021, 0.050]	[0.019, 0.049]	[-0.006, 0.034]		
p-value	<0.001***	<0.001***	0.176		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.019, 0.022] 0.864
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.003, 0.046] 0.089
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.045, 0.005] 0.125

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and

baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.047	0.030	0.028		
[95% CI]	[0.030, 0.064]	[0.012, 0.048]	[0.003, 0.052]		
p-value	<0.001***	0.001**	0.029*		
CHF 5993 pMDI - CHF 1535 pMDI					0.017 [-0.008, 0.042] 0.178
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.011, 0.050] 0.208
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.033, 0.028] 0.884
Visit 5 (Week 26)					
Adjusted Mean	0.052	0.049	0.039		
[95% CI]	[0.036, 0.069]	[0.032, 0.067]	[0.015, 0.063]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.021, 0.027] 0.794
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.016, 0.043] 0.362
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.040, 0.019] 0.492

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.062	0.054	0.026		
[95% CI]	[0.045, 0.080]	[0.036, 0.072]	[0.001, 0.051]		
p-value	<0.001***	<0.001***	0.046*		
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.017, 0.034] 0.532
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.036 [0.005, 0.067] 0.022*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.060, 0.003] 0.079
Visit 7 (Week 52)					
Adjusted Mean	0.078	0.065	0.044		
[95% CI]	[0.062, 0.095]	[0.048, 0.082]	[0.021, 0.068]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.010, 0.037] 0.261
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.034 [0.005, 0.063] 0.021*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.050, 0.009] 0.170

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.010, 0.028] 0.364
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.026 [0.002, 0.049] 0.031*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.041, 0.007] 0.162
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.048	0.041	0.032		
[95% CI]	[0.034, 0.062]	[0.027, 0.055]	[0.012, 0.051]		
p-value	<0.001***	<0.001***	0.002**		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.059	0.050	0.033		
[95% CI]	[0.046, 0.072]	[0.036, 0.064]	[0.014, 0.052]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.405	
Visit Period				<0.001***	
Treatment*Visit Period				0.738	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.014	4.047	3.454		
[95% CI]	[2.853, 5.175]	[2.839, 5.255]	[1.794, 5.113]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.033 [-1.708, 1.642] 0.969
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.560 [-1.466, 2.586] 0.587
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.593 [-2.646, 1.460] 0.571

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.921	4.882	5.555		
[95% CI]	[4.557, 7.286]	[3.463, 6.300]	[3.595, 7.515]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.040 [-0.928, 3.008] 0.300
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.366 [-2.023, 2.755] 0.764
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.674 [-1.746, 3.094] 0.585
Visit 5 (Week 26)					
Adjusted Mean	6.943	5.266	5.725		
[95% CI]	[5.565, 8.321]	[3.836, 6.696]	[3.744, 7.706]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.677 [-0.309, 3.663] 0.098
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.218 [-1.196, 3.633] 0.322
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.459 [-1.985, 2.903] 0.713

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	7.787	7.010	6.423		
[95% CI]	[6.323, 9.251]	[5.493, 8.527]	[4.316, 8.531]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.777 [-1.332, 2.885] 0.470
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.364 [-1.203, 3.931] 0.297
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.587 [-3.184, 2.010] 0.657
Visit 7 (Week 52)					
Adjusted Mean	9.091	7.674	7.605		
[95% CI]	[7.639, 10.543]	[6.173, 9.175]	[5.511, 9.699]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.417 [-0.671, 3.506] 0.183
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.486 [-1.064, 4.035] 0.253
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.069 [-2.645, 2.508] 0.958

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					1.145 [-0.534, 2.825] 0.181
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.137 [-0.903, 3.178] 0.274
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-2.058, 2.074] 0.994
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.178	4.960	5.323		
[95% CI]	[5.018, 7.338]	[3.755, 6.165]	[3.659, 6.988]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.283	6.138	6.146		
[95% CI]	[6.118, 8.449]	[4.929, 7.348]	[4.472, 7.820]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL EQ5D Index					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.624	
Visit Period				0.021*	
Treatment*Visit Period				0.264	
Baseline				<0.001***	
Baseline*Visit Period				0.192	
Visit 3 (Week 4)					
Adjusted Mean	0.044	0.041	0.039		
[95% CI]	[0.029, 0.059]	[0.026, 0.056]	[0.017, 0.060]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.019, 0.024] 0.804
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.021, 0.032] 0.691
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.029, 0.024] 0.842

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and

baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.060	0.050	0.033		
[95% CI]	[0.044, 0.076]	[0.035, 0.066]	[0.011, 0.056]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.013, 0.032] 0.393
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-0.001, 0.055] 0.059
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.045, 0.010] 0.223
Visit 5 (Week 26)					
Adjusted Mean	0.065	0.053	0.068		
[95% CI]	[0.048, 0.081]	[0.037, 0.069]	[0.045, 0.091]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.011, 0.035] 0.307
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.003 [-0.031, 0.026] 0.852
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.015 [-0.013, 0.043] 0.305

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.068	0.056	0.068		
[95% CI]	[0.051, 0.084]	[0.040, 0.072]	[0.044, 0.091]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.011, 0.035] 0.318
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.029, 0.029] 0.996
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.017, 0.040] 0.416
Visit 7 (Week 52)					
Adjusted Mean	0.067	0.064	0.052		
[95% CI]	[0.050, 0.084]	[0.047, 0.080]	[0.028, 0.076]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.021, 0.027] 0.788
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.015, 0.045] 0.324
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.012 [-0.041, 0.018] 0.435

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.010, 0.028] 0.355
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.007 [-0.016, 0.031] 0.538
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.002 [-0.021, 0.025] 0.893
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.060	0.050	0.053		
[95% CI]	[0.046, 0.074]	[0.037, 0.064]	[0.033, 0.072]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.064	0.055	0.056		
[95% CI]	[0.050, 0.077]	[0.042, 0.068]	[0.038, 0.075]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.991	
Visit Period				<0.001***	
Treatment*Visit Period				0.165	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.512	3.995	3.920		
[95% CI]	[3.325, 5.699]	[2.850, 5.141]	[2.265, 5.574]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.517 [-1.133, 2.166] 0.539
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.592 [-1.444, 2.628] 0.568
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.076 [-2.089, 1.938] 0.941

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.483	6.722	5.095		
[95% CI]	[4.095, 6.871]	[5.385, 8.059]	[3.163, 7.028]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.239 [-3.167, 0.689] 0.207
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.387 [-1.992, 2.767] 0.749
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.626 [-3.977, 0.724] 0.175
Visit 5 (Week 26)					
Adjusted Mean	7.782	7.315	7.560		
[95% CI]	[6.367, 9.196]	[5.944, 8.685]	[5.584, 9.535]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.467 [-1.502, 2.436] 0.642
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.222 [-2.208, 2.651] 0.858
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.245 [-2.160, 2.651] 0.841

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	8.399	8.239	9.869		
[95% CI]	[7.019, 9.780]	[6.907, 9.572]	[7.943, 11.795]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.160 [-1.759, 2.079] 0.870
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-1.470 [-3.840, 0.900] 0.224
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.630 [-0.714, 3.973] 0.173
Visit 7 (Week 52)					
Adjusted Mean	9.873	9.622	10.065		
[95% CI]	[8.457, 11.289]	[8.257, 10.988]	[8.084, 12.046]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.251 [-1.716, 2.219] 0.802
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.191 [-2.626, 2.244] 0.877
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.443 [-1.964, 2.849] 0.718

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.076 [-1.526, 1.678] 0.926
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.275 [-2.253, 1.703] 0.785
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.351 [-1.605, 2.307] 0.725
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.571	6.622	6.241		
[95% CI]	[5.396, 7.747]	[5.486, 7.757]	[4.602, 7.881]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1)
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.825	7.750	8.100		
[95% CI]	[6.673, 8.978]	[6.637, 8.862]	[6.493, 9.708]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12f Statistical Analysis of EQ-5D-3L score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
EQ5D Index					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.067	
Visit Period				0.125	
Treatment*Visit Period				0.536	
Baseline				<0.001***	
Baseline*Visit Period				0.193	
Visit 3 (Week 4)					
Adjusted Mean	0.048	0.028	0.023		
[95% CI]	[0.025, 0.071]	[0.006, 0.050]	[-0.007, 0.053]		
p-value	<0.001***	0.015*	0.131		
CHF 5993 pMDI - CHF 1535 pMDI					0.020 [-0.012, 0.052] 0.214
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.013, 0.062] 0.203
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.004 [-0.042, 0.033] 0.816

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.065	0.032	-0.001		
[95% CI]	[0.036, 0.094]	[0.004, 0.060]	[-0.040, 0.037]		
p-value	<0.001***	0.027*	0.940		
CHF 5993 pMDI - CHF 1535 pMDI					0.033 [-0.007, 0.074] 0.106
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.066 [0.018, 0.114] 0.007**
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.080, 0.014] 0.172
Visit 5 (Week 26)					
Adjusted Mean	0.067	0.057	0.034		
[95% CI]	[0.041, 0.093]	[0.031, 0.082]	[0.000, 0.068]		
p-value	<0.001***	<0.001***	0.050*		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.026, 0.046] 0.570
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.033 [-0.010, 0.076] 0.132
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.022 [-0.065, 0.020] 0.299

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.066	0.065	0.022		
[95% CI]	[0.039, 0.093]	[0.039, 0.092]	[-0.014, 0.057]		
p-value	<0.001***	<0.001***	0.233		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.037, 0.039] 0.957
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.044 [-0.000, 0.089] 0.052
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.043 [-0.088, 0.001] 0.055
Visit 7 (Week 52)					
Adjusted Mean	0.063	0.068	0.033		
[95% CI]	[0.035, 0.091]	[0.041, 0.095]	[-0.005, 0.070]		
p-value	<0.001***	<0.001***	0.085		
CHF 5993 pMDI - CHF 1535 pMDI					-0.005 [-0.044, 0.034] 0.812
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.031 [-0.016, 0.077] 0.194
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.082, 0.010] 0.130

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.021, 0.038] 0.566
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.040 [0.005, 0.075] 0.026*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.066, 0.004] 0.078
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.063	0.044	0.022		
[95% CI]	[0.041, 0.085]	[0.023, 0.066]	[-0.008, 0.051]		
p-value	<0.001***	<0.001***	0.148		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.064	0.055	0.024		
[95% CI]	[0.043, 0.085]	[0.035, 0.076]	[-0.004, 0.052]		
p-value	<0.001***	<0.001***	0.092		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.729	
Visit Period				<0.001***	
Treatment*Visit Period				0.249	
Baseline				<0.001***	
Baseline*Visit Period				0.015*	
Visit 3 (Week 4)					
Adjusted Mean	4.295	3.680	4.569		
[95% CI]	[2.366, 6.224]	[1.815, 5.546]	[2.031, 7.108]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.615 [-2.069, 3.298] 0.653
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.274 [-3.462, 2.914] 0.866
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.889 [-2.263, 4.040] 0.579

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	6.038	6.313	4.510		
[95% CI]	[3.871, 8.206]	[4.211, 8.415]	[1.643, 7.377]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.275 [-3.294, 2.744] 0.858
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.528 [-2.066, 5.123] 0.404
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.803 [-5.359, 1.753] 0.319
Visit 5 (Week 26)					
Adjusted Mean	8.696	7.071	6.821		
[95% CI]	[6.463, 10.928]	[4.904, 9.239]	[3.871, 9.770]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.625 [-1.487, 4.736] 0.305
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.875 [-1.824, 5.574] 0.319
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.250 [-3.912, 3.411] 0.893

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	9.389	7.490	10.206		
[95% CI]	[7.219, 11.559]	[5.374, 9.605]	[7.338, 13.075]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.900 [-1.131, 4.930] 0.218
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.817 [-4.415, 2.780] 0.655
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					2.717 [-0.849, 6.283] 0.135
Visit 7 (Week 52)					
Adjusted Mean	9.941	9.120	10.909		
[95% CI]	[7.715, 12.166]	[6.960, 11.279]	[7.961, 13.856]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.821 [-2.280, 3.922] 0.603
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.968 [-4.662, 2.726] 0.607
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.789 [-1.866, 5.444] 0.336

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					1.143 [-1.351, 3.638] 0.368
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.275 [-2.691, 3.242] 0.855
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.868 [-2.067, 3.803] 0.561
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	7.201	6.316	5.763		
[95% CI]	[5.321, 9.081]	[4.494, 8.138]	[3.282, 8.245]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	8.422	7.279	8.147		
[95% CI]	[6.632, 10.212]	[5.542, 9.016]	[5.782, 10.512]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
EQ5D Index					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.552	
Visit Period				<0.001***	
Treatment*Visit Period				0.312	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	0.037	0.041	0.028		
[95% CI]	[0.025, 0.049]	[0.029, 0.053]	[0.010, 0.045]		
p-value	<0.001***	<0.001***	0.002**		
CHF 5993 pMDI - CHF 1535 pMDI					-0.004 [-0.021, 0.013] 0.665
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.011, 0.031] 0.357
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.034, 0.007] 0.206

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.049	0.044	0.041		
[95% CI]	[0.036, 0.062]	[0.031, 0.056]	[0.023, 0.060]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.012, 0.024] 0.538
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.015, 0.030] 0.496
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.002 [-0.025, 0.020] 0.856
Visit 5 (Week 26)					
Adjusted Mean	0.055	0.050	0.060		
[95% CI]	[0.042, 0.069]	[0.036, 0.063]	[0.041, 0.079]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.013, 0.025] 0.537
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.028, 0.019] 0.716
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.010 [-0.013, 0.034] 0.391

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.064	0.052	0.055		
[95% CI]	[0.050, 0.078]	[0.038, 0.066]	[0.036, 0.075]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.007, 0.032] 0.220
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.016, 0.033] 0.488
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.021, 0.028] 0.768
Visit 7 (Week 52)					
Adjusted Mean	0.075	0.063	0.054		
[95% CI]	[0.062, 0.088]	[0.050, 0.076]	[0.035, 0.073]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.006, 0.031] 0.192
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.002, 0.044] 0.068
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.032, 0.014] 0.441

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.008 [-0.007, 0.023] 0.284
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.011, 0.027] 0.403
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.000 [-0.019, 0.019] 0.976
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.051	0.046	0.049		
[95% CI]	[0.040, 0.062]	[0.035, 0.057]	[0.033, 0.065]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.060	0.052	0.052		
[95% CI]	[0.049, 0.071]	[0.041, 0.062]	[0.037, 0.067]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.740	
Visit Period				<0.001***	
Treatment*Visit Period				0.638	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.251	4.135	3.359		
[95% CI]	[3.342, 5.160]	[3.212, 5.058]	[2.044, 4.674]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.116 [-1.179, 1.411] 0.860
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.892 [-0.707, 2.492] 0.274
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.776 [-2.383, 0.831] 0.344

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.617	5.680	5.617		
[95% CI]	[4.532, 6.702]	[4.581, 6.779]	[4.045, 7.188]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.063 [-1.607, 1.481] 0.936
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-1.910, 1.911] 1.000
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.063 [-1.981, 1.854] 0.948
Visit 5 (Week 26)					
Adjusted Mean	6.931	6.085	6.556		
[95% CI]	[5.833, 8.030]	[4.971, 7.200]	[4.962, 8.151]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.846 [-0.718, 2.410] 0.289
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.375 [-1.562, 2.312] 0.704
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.471 [-1.475, 2.417] 0.635

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	7.672	7.707	7.342		
[95% CI]	[6.530, 8.815]	[6.553, 8.861]	[5.683, 9.002]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.035 [-1.658, 1.589] 0.967
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.330 [-1.685, 2.345] 0.748
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.364 [-2.386, 1.657] 0.724
Visit 7 (Week 52)					
Adjusted Mean	9.325	8.540	8.046		
[95% CI]	[8.182, 10.467]	[7.386, 9.693]	[6.382, 9.709]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.785 [-0.839, 2.409] 0.343
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.279 [-0.740, 3.297] 0.214
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.494 [-2.519, 1.531] 0.632

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.399 [-0.919, 1.716] 0.553
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.554 [-1.078, 2.185] 0.506
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.155 [-1.793, 1.483] 0.853
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.115	5.661	5.775		
[95% CI]	[5.199, 7.030]	[4.732, 6.589]	[4.448, 7.103]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.275	6.876	6.721		
[95% CI]	[6.349, 8.201]	[5.939, 7.813]	[5.378, 8.064]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12g Statistical Analysis of EQ-5D-3L score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
EQ5D Index					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.156	
Visit Period				0.006**	
Treatment*Visit Period				0.197	
Baseline				<0.001***	
Baseline*Visit Period				0.050*	
Visit 3 (Week 4)					
Adjusted Mean	0.042	0.041	0.023		
[95% CI]	[0.026, 0.057]	[0.026, 0.057]	[0.000, 0.045]		
p-value	<0.001***	<0.001***	0.047*		
CHF 5993 pMDI - CHF 1535 pMDI					0.000 [-0.022, 0.022] 0.988
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.009, 0.046] 0.185
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.046, 0.009] 0.186

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and

baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.053	0.039	0.038		
[95% CI]	[0.036, 0.071]	[0.022, 0.056]	[0.013, 0.063]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					0.014 [-0.010, 0.039] 0.256
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.016, 0.046] 0.328
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.001 [-0.032, 0.030] 0.947
Visit 5 (Week 26)					
Adjusted Mean	0.059	0.057	0.054		
[95% CI]	[0.041, 0.077]	[0.039, 0.074]	[0.028, 0.079]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.003 [-0.022, 0.028] 0.825
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.025, 0.037] 0.714
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.034, 0.028] 0.850

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.064	0.059	0.032		
[95% CI]	[0.046, 0.083]	[0.041, 0.077]	[0.006, 0.058]		
p-value	<0.001***	<0.001***	0.017*		
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.021, 0.031] 0.686
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.032 [0.000, 0.064] 0.049*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.027 [-0.059, 0.005] 0.098
Visit 7 (Week 52)					
Adjusted Mean	0.072	0.066	0.027		
[95% CI]	[0.054, 0.090]	[0.048, 0.083]	[0.002, 0.053]		
p-value	<0.001***	<0.001***	0.037*		
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.019, 0.031] 0.636
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.045 [0.013, 0.076] 0.005**
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.038 [-0.070, -0.007] 0.015*

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.006 [-0.014, 0.026] 0.571
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.024 [-0.001, 0.049] 0.057
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.043, 0.006] 0.145
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.055	0.049	0.044		
[95% CI]	[0.040, 0.069]	[0.034, 0.063]	[0.023, 0.065]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.061	0.055	0.037		
[95% CI]	[0.047, 0.076]	[0.041, 0.069]	[0.016, 0.057]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.422	
Visit Period				<0.001***	
Treatment*Visit Period				0.603	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.349	3.702	3.771		
[95% CI]	[3.140, 5.558]	[2.517, 4.886]	[2.045, 5.498]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.647 [-1.044, 2.339] 0.453
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.578 [-1.531, 2.687] 0.591
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.070 [-2.025, 2.164] 0.948

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.684	5.314	5.659		
[95% CI]	[4.260, 7.109]	[3.916, 6.712]	[3.618, 7.700]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.370 [-1.626, 2.366] 0.716
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-2.465, 2.516] 0.984
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.345 [-2.129, 2.819] 0.784
Visit 5 (Week 26)					
Adjusted Mean	7.100	5.854	5.372		
[95% CI]	[5.615, 8.586]	[4.392, 7.317]	[3.249, 7.494]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.246 [-0.838, 3.330] 0.241
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.729 [-0.864, 4.322] 0.191
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.483 [-3.061, 2.095] 0.713

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	8.269	6.837	8.242		
[95% CI]	[6.713, 9.825]	[5.310, 8.364]	[6.027, 10.457]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.432 [-0.749, 3.612] 0.198
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.027 [-2.682, 2.736] 0.984
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					1.405 [-1.285, 4.095] 0.305
Visit 7 (Week 52)					
Adjusted Mean	9.652	7.853	8.454		
[95% CI]	[8.096, 11.207]	[6.333, 9.372]	[6.252, 10.655]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.799 [-0.376, 3.974] 0.105
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.198 [-1.500, 3.895] 0.384
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.601 [-2.074, 3.276] 0.659

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					1.243 [-0.518, 3.004] 0.166
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.797 [-1.394, 2.989] 0.475
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.445 [-1.732, 2.622] 0.688
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.241	5.357	5.214		
[95% CI]	[4.998, 7.484]	[4.136, 6.578]	[3.436, 6.991]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.574	6.331	6.777		
[95% CI]	[6.318, 8.831]	[5.098, 7.565]	[4.983, 8.570]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No EQ5D Index					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.510	
Visit Period				<0.001***	
Treatment*Visit Period				0.607	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	0.038	0.035	0.029		
[95% CI]	[0.024, 0.051]	[0.021, 0.049]	[0.009, 0.048]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.017, 0.022] 0.816
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.015, 0.033] 0.469
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.030, 0.018] 0.600

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and

baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.052	0.043	0.023		
[95% CI]	[0.036, 0.067]	[0.027, 0.059]	[0.001, 0.045]		
p-value	<0.001***	<0.001***	0.041*		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.014, 0.031] 0.455
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.029 [0.002, 0.056] 0.038*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.047, 0.007] 0.148
Visit 5 (Week 26)					
Adjusted Mean	0.056	0.047	0.052		
[95% CI]	[0.041, 0.071]	[0.032, 0.063]	[0.031, 0.074]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.013, 0.031] 0.409
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.022, 0.030] 0.763
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.005 [-0.021, 0.032] 0.705

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.064	0.052	0.060		
[95% CI]	[0.048, 0.080]	[0.036, 0.068]	[0.037, 0.082]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.012 [-0.011, 0.035] 0.299
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.023, 0.032] 0.759
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.020, 0.035] 0.585
Visit 7 (Week 52)					
Adjusted Mean	0.072	0.064	0.067		
[95% CI]	[0.057, 0.088]	[0.048, 0.079]	[0.045, 0.089]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.013, 0.030] 0.441
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.005 [-0.021, 0.032] 0.689
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.003 [-0.024, 0.030] 0.818

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.009 [-0.008, 0.027] 0.305
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.013, 0.030] 0.426
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.021, 0.022] 0.957
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.052	0.044	0.040		
[95% CI]	[0.039, 0.065]	[0.031, 0.057]	[0.022, 0.058]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.060	0.051	0.051		
[95% CI]	[0.048, 0.072]	[0.038, 0.063]	[0.034, 0.069]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.860	
Visit Period				<0.001***	
Treatment*Visit Period				0.588	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	4.144	4.400	3.566		
[95% CI]	[3.011, 5.277]	[3.237, 5.563]	[1.980, 5.152]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.256 [-1.880, 1.368] 0.757
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.578 [-1.372, 2.527] 0.561
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.834 [-2.801, 1.134] 0.406

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	5.713	6.408	4.991		
[95% CI]	[4.393, 7.034]	[5.057, 7.758]	[3.140, 6.842]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.695 [-2.584, 1.194] 0.470
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.722 [-1.551, 2.996] 0.533
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.417 [-3.709, 0.875] 0.225
Visit 5 (Week 26)					
Adjusted Mean	7.541	6.831	7.736		
[95% CI]	[6.248, 8.835]	[5.509, 8.154]	[5.912, 9.560]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.710 [-1.140, 2.560] 0.451
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.195 [-2.431, 2.041] 0.864
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.905 [-1.349, 3.158] 0.431

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	7.815	8.519	7.943		
[95% CI]	[6.525, 9.106]	[7.202, 9.837]	[6.114, 9.772]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.704 [-2.549, 1.141] 0.454
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.128 [-2.366, 2.110] 0.911
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.576 [-2.831, 1.679] 0.616
Visit 7 (Week 52)					
Adjusted Mean	9.235	9.570	9.139		
[95% CI]	[7.928, 10.543]	[8.233, 10.906]	[7.268, 11.010]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.335 [-2.205, 1.535] 0.725
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.096 [-2.186, 2.378] 0.934
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.431 [-2.730, 1.869] 0.713

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					-0.202 [-1.706, 1.302] 0.792
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.091 [-1.726, 1.908] 0.922
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.293 [-2.125, 1.538] 0.753
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	6.456	6.327	6.250		
[95% CI]	[5.376, 7.537]	[5.221, 7.433]	[4.732, 7.768]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	7.463	7.666	7.373		
[95% CI]	[6.412, 8.515]	[6.590, 8.741]	[5.891, 8.854]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12h Statistical Analysis of EQ-5D-3L score by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
EQ5D Index					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.307	
Visit Period				<0.001***	
Treatment*Visit Period				0.582	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	0.029	0.031	0.015		
[95% CI]	[0.016, 0.041]	[0.018, 0.043]	[-0.003, 0.033]		
p-value	<0.001***	<0.001***	0.096		
CHF 5993 pMDI - CHF 1535 pMDI					-0.002 [-0.020, 0.016] 0.828
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.009, 0.035] 0.233
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.015 [-0.037, 0.007] 0.172

Produced: 17 December 2020 Page 1 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.042	0.031	0.017		
[95% CI]	[0.027, 0.056]	[0.017, 0.045]	[-0.003, 0.037]		
p-value	<0.001***	<0.001***	0.098		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.010, 0.031] 0.309
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.025 [-0.000, 0.049] 0.051
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.014 [-0.039, 0.011] 0.263
Visit 5 (Week 26)					
Adjusted Mean	0.039	0.039	0.036		
[95% CI]	[0.024, 0.053]	[0.024, 0.054]	[0.015, 0.057]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.000 [-0.021, 0.021] 0.969
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.002 [-0.023, 0.028] 0.850
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.029, 0.023] 0.825

Produced: 17 December 2020 Page 2 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.050	0.038	0.031		
[95% CI]	[0.034, 0.065]	[0.023, 0.053]	[0.010, 0.053]		
p-value	<0.001***	<0.001***	0.004**		
CHF 5993 pMDI - CHF 1535 pMDI					0.011 [-0.010, 0.033] 0.291
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.008, 0.044] 0.176
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.033, 0.020] 0.622
Visit 7 (Week 52)					
Adjusted Mean	0.052	0.051	0.035		
[95% CI]	[0.037, 0.067]	[0.036, 0.065]	[0.014, 0.056]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.019, 0.022] 0.887
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.017 [-0.008, 0.043] 0.184
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.041, 0.010] 0.224

Produced: 17 December 2020 Page 3 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.005 [-0.012, 0.021] 0.573
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.014 [-0.006, 0.035] 0.169
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.030, 0.011] 0.359
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.038	0.035	0.027		
[95% CI]	[0.026, 0.050]	[0.023, 0.048]	[0.010, 0.044]		
p-value	<0.001***	<0.001***	0.002**		

Produced: 17 December 2020 Page 4 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.044	0.040	0.030		
[95% CI]	[0.033, 0.056]	[0.028, 0.051]	[0.013, 0.047]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 5 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.906	
Visit Period				<0.001***	
Treatment*Visit Period				0.438	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	3.904	3.733	2.651		
[95% CI]	[2.812, 4.997]	[2.637, 4.829]	[1.107, 4.196]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.171 [-1.376, 1.719] 0.828
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.253 [-0.639, 3.145] 0.194
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.082 [-2.977, 0.814] 0.263

Produced: 17 December 2020 Page 6 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	4.419	5.659	3.975		
[95% CI]	[3.125, 5.713]	[4.364, 6.955]	[2.139, 5.811]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-1.240 [-3.070, 0.591] 0.184
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.444 [-1.803, 2.691] 0.698
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-1.684 [-3.932, 0.564] 0.142
Visit 5 (Week 26)					
Adjusted Mean	5.960	6.104	6.193		
[95% CI]	[4.664, 7.256]	[4.806, 7.402]	[4.349, 8.037]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.144 [-1.978, 1.690] 0.878
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.233 [-2.488, 2.022] 0.839
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.089 [-2.167, 2.346] 0.938

Produced: 17 December 2020 Page 7 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	6.555	6.751	7.215		
[95% CI]	[5.243, 7.867]	[5.440, 8.063]	[5.348, 9.083]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.196 [-2.051, 1.658] 0.836
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.660 [-2.943, 1.623] 0.570
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.464 [-1.820, 2.748] 0.690
Visit 7 (Week 52)					
Adjusted Mean	7.961	7.626	7.973		
[95% CI]	[6.692, 9.230]	[6.360, 8.893]	[6.159, 9.786]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.335 [-1.458, 2.127] 0.714
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.012 [-2.226, 2.202] 0.992
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.347 [-1.867, 2.560] 0.759

Produced: 17 December 2020 Page 8 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
<hr/>					
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					-0.192 [-1.681, 1.297] 0.800
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.079 [-1.908, 1.751] 0.933
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.113 [-1.944, 1.717] 0.903
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	5.170	5.602	4.966		
[95% CI]	[4.094, 6.245]	[4.525, 6.680]	[3.440, 6.492]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 9 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	6.187	6.379	6.265		
[95% CI]	[5.134, 7.239]	[5.325, 7.432]	[4.770, 7.761]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 10 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
EQ5D Index					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.299	
Visit Period				0.011*	
Treatment*Visit Period				0.796	
Baseline				<0.001***	
Baseline*Visit Period				0.131	
Visit 3 (Week 4)					
Adjusted Mean	0.054	0.047	0.040		
[95% CI]	[0.036, 0.071]	[0.029, 0.064]	[0.016, 0.065]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.018, 0.032] 0.581
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.013 [-0.017, 0.044] 0.385
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.037, 0.024] 0.676

Produced: 17 December 2020 Page 11 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 4 (Week 12)					
Adjusted Mean	0.067	0.052	0.047		
[95% CI]	[0.047, 0.087]	[0.032, 0.072]	[0.019, 0.075]		
p-value	<0.001***	<0.001***	0.001**		
CHF 5993 pMDI - CHF 1535 pMDI					0.015 [-0.014, 0.043] 0.310
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.015, 0.054] 0.259
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.005 [-0.040, 0.029] 0.765
Visit 5 (Week 26)					
Adjusted Mean	0.082	0.067	0.074		
[95% CI]	[0.063, 0.101]	[0.048, 0.086]	[0.048, 0.101]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.016 [-0.011, 0.042] 0.253
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.025, 0.041] 0.629
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.008 [-0.025, 0.040] 0.652

Produced: 17 December 2020 Page 12 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Visit 6 (Week 40)					
Adjusted Mean	0.083	0.077	0.065		
[95% CI]	[0.063, 0.103]	[0.056, 0.097]	[0.037, 0.093]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.007 [-0.022, 0.035] 0.651
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.018 [-0.017, 0.053] 0.312
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.046, 0.023] 0.522
Visit 7 (Week 52)					
Adjusted Mean	0.099	0.082	0.064		
[95% CI]	[0.080, 0.119]	[0.062, 0.101]	[0.037, 0.092]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.018 [-0.010, 0.045] 0.212
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.035 [0.001, 0.069] 0.044*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.017 [-0.051, 0.017] 0.317

Produced: 17 December 2020 Page 13 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					0.013 [-0.009, 0.035] 0.256
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.019 [-0.008, 0.046] 0.165
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.033, 0.021] 0.647
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	0.073	0.059	0.061		
[95% CI]	[0.057, 0.089]	[0.043, 0.075]	[0.038, 0.083]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 14 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
EQ5D Index					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	0.082	0.069	0.063		
[95% CI]	[0.066, 0.097]	[0.053, 0.085]	[0.041, 0.085]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 15 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.319	
Visit Period				<0.001***	
Treatment*Visit Period				0.534	
Baseline				<0.001***	
Baseline*Visit Period				0.002**	
Visit 3 (Week 4)					
Adjusted Mean	4.708	4.397	4.958		
[95% CI]	[3.439, 5.978]	[3.123, 5.671]	[3.163, 6.753]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.311 [-1.487, 2.110] 0.734
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.249 [-2.448, 1.949] 0.824
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.561 [-1.641, 2.762] 0.617

Produced: 17 December 2020 Page 16 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 4 (Week 12)					
Adjusted Mean	7.348	6.052	7.024		
[95% CI]	[5.875, 8.822]	[4.572, 7.531]	[4.940, 9.108]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.297 [-0.791, 3.385] 0.223
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.325 [-2.228, 2.877] 0.803
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.972 [-1.584, 3.528] 0.455
Visit 5 (Week 26)					
Adjusted Mean	9.063	6.588	7.205		
[95% CI]	[7.541, 10.585]	[5.055, 8.122]	[5.051, 9.360]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					2.474 [0.314, 4.635] 0.025*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.857 [-0.781, 4.495] 0.167
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.617 [-2.027, 3.261] 0.647

Produced: 17 December 2020 Page 17 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Visit 6 (Week 40)					
Adjusted Mean	9.970	8.791	9.227		
[95% CI]	[8.390, 11.551]	[7.204, 10.377]	[6.991, 11.463]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.180 [-1.060, 3.419] 0.301
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.743 [-1.995, 3.481] 0.594
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.436 [-2.305, 3.178] 0.755
Visit 7 (Week 52)					
Adjusted Mean	11.370	10.017	9.826		
[95% CI]	[9.714, 13.025]	[8.358, 11.677]	[7.485, 12.168]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					1.352 [-0.992, 3.696] 0.258
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.543 [-1.325, 4.411] 0.291
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.191 [-3.061, 2.679] 0.896

Produced: 17 December 2020 Page 18 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall					
CHF 5993 pMDI - CHF 1535 pMDI					1.519 [-0.325, 3.363] 0.106
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					1.087 [-1.167, 3.341] 0.344
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.432 [-1.825, 2.690] 0.707
Overall 26-week period (Weeks 1-26)					
Adjusted Mean	7.865	6.086	6.804		
[95% CI]	[6.583, 9.148]	[4.797, 7.376]	[4.989, 8.618]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 19 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					
Overall 52-week period (Weeks 1-52)					
Adjusted Mean	9.241	7.721	8.154		
[95% CI]	[7.940, 10.542]	[6.414, 9.028]	[6.313, 9.994]		
p-value	<0.001***	<0.001***	<0.001***		

Produced: 17 December 2020 Page 20 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 20.2.12i Statistical Analysis of EQ-5D-3L score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
VAS Score					

Produced: 17 December 2020 Page 25 of 20

Source: Listing Not Applicable

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

ADDITIONAL_TLF_BATCH2_ACQ5

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch2

Date of Production: 17/12/2020

Identification Code: Additional_TLF_batch2_ACQ5_CCD-05993AB2-02_20201217(Batch2)

Table 18.2.11a Statistical Analysis of ACQ-5 total score including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.367
Visit Period			0.120
Treatment*Visit Period			0.565
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Age Group			0.710
Age Group Treatment Interaction			0.500

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11b Statistical Analysis of ACQ-5 total score including Gender - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.854
Visit Period			0.121
Treatment*Visit Period			0.565
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Gender			0.413
Gender Treatment Interaction			0.089

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11c Statistical Analysis of ACQ-5 total score including BMI Class - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.592
Visit Period			0.121
Treatment*Visit Period			0.568
Baseline			<0.001***
Baseline*Visit Period			<0.001***
BMI Class			0.261
BMI Class Treatment Interaction			0.846

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11d Statistical Analysis of ACQ-5 total score including Smoking Status - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.759
Visit Period			0.120
Treatment*Visit Period			0.564
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Smoking Status			0.129
Smoking Status Treatment Interaction			0.830

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11e Statistical Analysis of ACQ-5 total score including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.938
Visit Period			0.120
Treatment*Visit Period			0.566
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Number of Exacerbation in the Previous year			0.614
Number of Exacerbation in the Previous year Treatment Interaction			0.288

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11f Statistical Analysis of ACQ-5 total score including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.527
Visit Period			0.113
Treatment*Visit Period			0.568
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Degree of reversibility at screening (delta FEV1)			0.090
Degree of reversibility at screening (delta FEV1)			0.172
Treatment Interaction			

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11g Statistical Analysis of ACQ-5 total score including Use of Spacer - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.886
Visit Period			0.120
Treatment*Visit Period			0.565
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Use of Spacer			0.060
Use of Spacer Treatment Interaction			0.348

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11h Statistical Analysis of ACQ-5 total score including Relevant Concomitant Cardiovascular Diseases - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.518
Visit Period			0.120
Treatment*Visit Period			0.568
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.056
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.928

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.11i Statistical Analysis of ACQ-5 total score including Region - Interaction Test
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
ACQ-5 total score			
Number of Patients Included in Model	569	285	
Effect			
Treatment			0.429
Visit Period			0.119
Treatment*Visit Period			0.566
Baseline			<0.001***
Baseline*Visit Period			<0.001***
Region			0.132
Region Treatment Interaction			0.139

Produced: 17 December 2020 Page 1 of 1

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.14a Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.061
Baseline			<0.001***
Age Group			0.586
Age Group Treatment Interaction			0.013

Produced: 17 December 2020 Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14a Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Age Group - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.146
Baseline			0.002
Age Group			0.367
Age Group Treatment Interaction			0.200

Produced: 17 December 2020 Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14b Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.880
Baseline			<0.001***
Gender			0.672
Gender Treatment Interaction			0.777

Produced: 17 December 2020 Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14b Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Gender - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.495
Baseline			0.002
Gender			0.720
Gender Treatment Interaction			0.644

Produced: 17 December 2020

Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.983
Baseline			<0.001***
BMI Class			0.698
BMI Class Treatment Interaction			0.437

Produced: 17 December 2020 Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including BMI Class - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.388
Baseline			0.001
BMI Class			0.736
BMI Class Treatment Interaction			0.060

Produced: 17 December 2020 Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14d Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.545
Baseline			<0.001***
Smoking Status			0.044
Smoking Status Treatment Interaction			0.534

Produced: 17 December 2020 Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14d Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Smoking Status - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.378
Baseline			0.003
Smoking Status			0.003
Smoking Status Treatment Interaction			0.686

Produced: 17 December 2020 Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14e Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.553
Baseline			<0.001***
Number of Exacerbation in the Previous year			0.233
Number of Exacerbation in the Previous year Treatment Interaction			0.209

Produced: 17 December 2020

Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14e Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Number of Exacerbation in the Previous year - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.632
Baseline			0.002
Number of Exacerbation in the Previous year			0.704
Number of Exacerbation in the Previous year Treatment Interaction			0.718

Produced: 17 December 2020 Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14f Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.826
Baseline			<0.001***
Degree of reversibility at screening (delta FEV1)			<0.001***
Degree of reversibility at screening (delta FEV1)			0.350
Treatment Interaction			

Produced: 17 December 2020

Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14f Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Degree of reversibility at screening (delta FEV1) - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.427
Baseline			0.002
Degree of reversibility at screening (delta FEV1)			0.014
Degree of reversibility at screening (delta FEV1)			0.267
Treatment Interaction			

Produced: 17 December 2020

Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14g Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Use of Spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.526
Baseline			<0.001***
Use of Spacer			0.686
Use of Spacer Treatment Interaction			0.434

Produced: 17 December 2020

Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14g Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Use of Spacer - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.411
Baseline			0.002
Use of Spacer			0.441
Use of Spacer Treatment Interaction			0.858

Produced: 17 December 2020

Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14h Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.792
Baseline			<0.001***
Relevant Concomitant Cardiovascular Diseases			0.170
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.788

Produced: 17 December 2020

Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14h Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.413
Baseline			0.001
Relevant Concomitant Cardiovascular Diseases			0.062
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.404

Produced: 17 December 2020

Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14i Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 5 (Week 26)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.628
Baseline			<0.001***
Region			0.670
Region Treatment Interaction			0.036

Produced: 17 December 2020

Page 1 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.14i Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) including Region - Interaction Test (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Visit 7 (Week 52)			
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.367
Baseline			0.002
Region			0.137
Region Treatment Interaction			0.360

Produced: 17 December 2020 Page 2 of 2

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	472	444	244		
Effect					
Treatment				0.421	
Visit Period				0.009**	
Treatment*Visit Period				0.666	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.602	-0.574	-0.602		
[95% CI]	[-0.666, -0.537]	[-0.640, -0.508]	[-0.692, -0.513]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.028 [-0.120, 0.065] 0.557
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.109, 0.111] 0.989
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.140, 0.083] 0.617

Produced: 17 December 2020

Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.747	-0.684	-0.769		
[95% CI]	[-0.815, -0.679]	[-0.754, -0.614]	[-0.864, -0.675]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.063 [-0.161, 0.034] 0.204
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.022 [-0.094, 0.139] 0.707
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.086 [-0.203, 0.032] 0.153
Visit 5 (Week 26)					
Adjusted Mean	-0.823	-0.778	-0.846		
[95% CI]	[-0.897, -0.750]	[-0.853, -0.703]	[-0.948, -0.744]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.151, 0.060] 0.398
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.023 [-0.103, 0.149] 0.719
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.068 [-0.195, 0.058] 0.290

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.873	-0.826	-0.839		
[95% CI]	[-0.948, -0.797]	[-0.902, -0.749]	[-0.943, -0.735]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.155, 0.061] 0.391
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.034 [-0.162, 0.095] 0.609
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.013 [-0.143, 0.116] 0.838
Visit 7 (Week 52)					
Adjusted Mean	-0.917	-0.822	-0.850		
[95% CI]	[-0.995, -0.840]	[-0.902, -0.743]	[-0.958, -0.742]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.095 [-0.206, 0.016] 0.093
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.067 [-0.200, 0.066] 0.324
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.162, 0.106] 0.681

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.830	-0.771	-0.815		
[95% CI]	[-0.892, -0.767]	[-0.835, -0.706]	[-0.902, -0.727]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.149, 0.032] 0.202
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.015 [-0.123, 0.093] 0.788
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-0.153, 0.065] 0.428

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	97	121	41		
Effect					
Treatment				0.181	
Visit Period				0.162	
Treatment*Visit Period				0.702	
Baseline				<0.001***	
Baseline*Visit Period				0.026*	
Visit 3 (Week 4)					
Adjusted Mean	-0.670	-0.507	-0.636		
[95% CI]	[-0.809, -0.531]	[-0.631, -0.383]	[-0.849, -0.423]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.163 [-0.349, 0.024] 0.086
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.034 [-0.289, 0.221] 0.793
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.129 [-0.375, 0.117] 0.303

Produced: 17 December 2020

Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.748	-0.670	-0.687		
[95% CI]	[-0.907, -0.589]	[-0.813, -0.526]	[-0.936, -0.439]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.079 [-0.293, 0.136] 0.471
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.061 [-0.356, 0.235] 0.686
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.018 [-0.305, 0.269] 0.902
Visit 5 (Week 26)					
Adjusted Mean	-0.958	-0.747	-0.709		
[95% CI]	[-1.118, -0.799]	[-0.891, -0.602]	[-0.962, -0.456]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.212 [-0.428, 0.004] 0.055
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.249 [-0.549, 0.050] 0.102
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.038 [-0.253, 0.329] 0.799

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.827	-0.675	-0.748		
[95% CI]	[-0.995, -0.658]	[-0.828, -0.522]	[-1.015, -0.482]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.151 [-0.380, 0.077] 0.193
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.078 [-0.394, 0.238] 0.627
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.073 [-0.380, 0.234] 0.639
Visit 7 (Week 52)					
Adjusted Mean	-0.983	-0.772	-0.828		
[95% CI]	[-1.145, -0.821]	[-0.919, -0.625]	[-1.084, -0.572]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.211 [-0.430, 0.009] 0.060
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.155 [-0.458, 0.149] 0.316
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.056 [-0.351, 0.239] 0.709

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12a Statistical Analysis of ACQ-5 total score by Age Group
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.874	-0.703	-0.738		
[95% CI]	[-1.009, -0.739]	[-0.825, -0.581]	[-0.950, -0.526]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.171 [-0.354, 0.012] 0.067
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.136 [-0.388, 0.116] 0.289
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.035 [-0.280, 0.209] 0.777

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13a ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Age Group
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Age Group: <65 years old	(N=473)	(N=448)	(N=246)
Visit 5 (Week 26)			
Responders	297 (52.0)	268 (46.9)	159 (55.4)
Non-Responders	176 (30.8)	180 (31.5)	87 (30.3)
Change > -0.5	175 (30.6)	179 (31.3)	87 (30.3)
Missing data	1 (0.2)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	296 (51.8)	273 (47.8)	150 (52.3)
Non-Responders	177 (31.0)	175 (30.6)	96 (33.4)
Change > -0.5	176 (30.8)	175 (30.6)	96 (33.4)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13a ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Age Group
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Age Group: >= 65 years old	(N=98)	(N=123)	(N=41)
Visit 5 (Week 26)			
Responders	70 (12.3)	70 (12.3)	20 (7.0)
Non-Responders	28 (4.9)	53 (9.3)	21 (7.3)
Change > -0.5	27 (4.7)	53 (9.3)	21 (7.3)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	71 (12.4)	76 (13.3)	24 (8.4)
Non-Responders	27 (4.7)	47 (8.2)	17 (5.9)
Change > -0.5	27 (4.7)	47 (8.2)	17 (5.9)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
[2] Table presents number and percentage of patients (n (%))
[3] Percentages are based on the number of patients in the relevant treatment/population (N)
[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15a Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Age Group: <65 years old					
Visit 5 (Week 26)					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.392	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.085 [0.826, 1.425] 0.559/ 1.011 [0.955, 1.071] 0.697/ 0.016 [-0.046, 0.079] 0.608
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.861 [0.619, 1.197] 0.374/ 0.981 [0.919, 1.048] 0.570/ -0.028 [-0.101, 0.045] 0.453
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.260 [0.905, 1.753] 0.171/ 1.031 [0.964, 1.103] 0.377/ 0.045 [-0.030, 0.119] 0.243

Produced: 17 December 2020

Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15a Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	473	448	246		
Effect					
Treatment				0.974	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.032 [0.788, 1.353] 0.817/ 0.998 [0.924, 1.078] 0.958/ -0.000 [-0.062, 0.062] 0.994
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.018 [0.738, 1.405] 0.913/ 1.005 [0.917, 1.101] 0.916/ 0.003 [-0.070, 0.075] 0.941
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.014 [0.733, 1.403] 0.932/ 0.993 [0.904, 1.091] 0.884/ -0.003 [-0.077, 0.071] 0.937

Produced: 17 December 2020

Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15a Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Age Group: >= 65 years old					
Visit 5 (Week 26)					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.031	
Baseline				0.065	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.823 [1.031, 3.222] 0.039*/ 1.218 [1.001, 1.482] 0.049*/ 0.132 [0.007, 0.257] 0.038*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.518 [1.180, 5.374] 0.017*/ 1.435 [1.025, 2.008] 0.036*/ 0.210 [0.035, 0.386] 0.019*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.724 [0.355, 1.478] 0.375/ 0.849 [0.600, 1.201] 0.354/ -0.078 [-0.252, 0.096] 0.381

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15a Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Age Group (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.179	
Baseline				0.545	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.604 [0.902, 2.851] 0.108/ 1.170 [0.973, 1.408] 0.095/ 0.104 [-0.019, 0.228] 0.097
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.832 [0.852, 3.939] 0.121/ 1.223 [0.918, 1.630] 0.169/ 0.134 [-0.042, 0.311] 0.135
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.875 [0.426, 1.799] 0.717/ 0.957 [0.713, 1.284] 0.769/ -0.030 [-0.204, 0.144] 0.736

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	242	101		
Effect					
Treatment				0.529	
Visit Period				0.749	
Treatment*Visit Period				0.227	
Baseline				<0.001***	
Baseline*Visit Period				0.030*	
Visit 3 (Week 4)					
Adjusted Mean	-0.512	-0.534	-0.675		
[95% CI]	[-0.607, -0.418]	[-0.623, -0.445]	[-0.812, -0.538]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.022 [-0.108, 0.151] 0.744
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.163 [-0.004, 0.330] 0.056
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.141 [-0.305, 0.022] 0.091

Produced: 17 December 2020

Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.656	-0.618	-0.772		
[95% CI]	[-0.758, -0.553]	[-0.714, -0.523]	[-0.920, -0.624]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.177, 0.103] 0.603
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.117 [-0.063, 0.297] 0.204
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.154 [-0.330, 0.023] 0.087
Visit 5 (Week 26)					
Adjusted Mean	-0.793	-0.685	-0.732		
[95% CI]	[-0.904, -0.682]	[-0.790, -0.581]	[-0.893, -0.572]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.108 [-0.260, 0.045] 0.165
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.061 [-0.256, 0.135] 0.541
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.047 [-0.239, 0.145] 0.630

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.787	-0.743	-0.774		
[95% CI]	[-0.900, -0.674]	[-0.849, -0.637]	[-0.938, -0.611]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.044 [-0.199, 0.111] 0.579
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.013 [-0.212, 0.186] 0.901
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.226, 0.164] 0.754
Visit 7 (Week 52)					
Adjusted Mean	-0.820	-0.750	-0.802		
[95% CI]	[-0.935, -0.706]	[-0.857, -0.643]	[-0.967, -0.637]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.071 [-0.227, 0.086] 0.375
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.018 [-0.219, 0.182] 0.857
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.052 [-0.249, 0.145] 0.603

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.755	-0.694	-0.761		
[95% CI]	[-0.851, -0.659]	[-0.784, -0.604]	[-0.900, -0.623]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.061 [-0.192, 0.070] 0.360
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.162, 0.175] 0.940
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.068 [-0.233, 0.098] 0.422

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	357	323	184		
Effect					
Treatment				0.257	
Visit Period				0.016*	
Treatment*Visit Period				0.701	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.672	-0.581	-0.569		
[95% CI]	[-0.745, -0.598]	[-0.659, -0.504]	[-0.672, -0.467]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.090 [-0.198, 0.017] 0.099
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.102 [-0.229, 0.024] 0.113
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.117, 0.141] 0.855

Produced: 17 December 2020

Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.800	-0.729	-0.750		
[95% CI]	[-0.879, -0.721]	[-0.812, -0.646]	[-0.860, -0.639]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.071 [-0.186, 0.043] 0.222
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.051 [-0.187, 0.085] 0.463
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.159, 0.117] 0.769
Visit 5 (Week 26)					
Adjusted Mean	-0.876	-0.839	-0.880		
[95% CI]	[-0.959, -0.793]	[-0.926, -0.752]	[-0.996, -0.764]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.037 [-0.157, 0.084] 0.551
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.139, 0.147] 0.954
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.041 [-0.186, 0.104] 0.581

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.907	-0.836	-0.855		
[95% CI]	[-0.993, -0.821]	[-0.926, -0.746]	[-0.976, -0.735]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.070 [-0.195, 0.054] 0.269
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.051 [-0.200, 0.097] 0.495
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.019 [-0.169, 0.131] 0.805
Visit 7 (Week 52)					
Adjusted Mean	-0.988	-0.863	-0.873		
[95% CI]	[-1.076, -0.899]	[-0.956, -0.771]	[-0.997, -0.749]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.124 [-0.253, 0.004] 0.058
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.114 [-0.267, 0.038] 0.141
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.164, 0.145] 0.902

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12b Statistical Analysis of ACQ-5 total score by Gender
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.883	-0.807	-0.828		
[95% CI]	[-0.953, -0.812]	[-0.881, -0.733]	[-0.926, -0.729]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.075 [-0.178, 0.027] 0.148
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.055 [-0.176, 0.066] 0.375
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.144, 0.103] 0.743

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13b ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Gender
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Gender: Male	(N=212)	(N=244)	(N=103)
Visit 5 (Week 26)			
Responders	135 (23.6)	134 (23.5)	65 (22.6)
Non-Responders	77 (13.5)	110 (19.3)	38 (13.2)
Change > -0.5	76 (13.3)	109 (19.1)	38 (13.2)
Missing data	1 (0.2)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	131 (22.9)	146 (25.6)	62 (21.6)
Non-Responders	81 (14.2)	98 (17.2)	41 (14.3)
Change > -0.5	81 (14.2)	98 (17.2)	41 (14.3)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
[2] Table presents number and percentage of patients (n (%))
[3] Percentages are based on the number of patients in the relevant treatment/population (N)
[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13b ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Gender
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Gender: Female	(N=359)	(N=327)	(N=184)
Visit 5 (Week 26)			
Responders	232 (40.6)	204 (35.7)	114 (39.7)
Non-Responders	127 (22.2)	123 (21.5)	70 (24.4)
Change > -0.5	126 (22.1)	123 (21.5)	70 (24.4)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	236 (41.3)	203 (35.6)	112 (39.0)
Non-Responders	123 (21.5)	124 (21.7)	72 (25.1)
Change > -0.5	122 (21.4)	124 (21.7)	72 (25.1)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15b Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value
Gender: Male					
Visit 5 (Week 26)					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.097	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.453 [0.992, 2.129] 0.055/ 1.140 [0.983, 1.321] 0.083/ 0.088 [-0.002, 0.178] 0.056
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.980 [0.598, 1.605] 0.935/ 1.002 [0.841, 1.195] 0.981/ 0.006 [-0.108, 0.119] 0.921
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.484 [0.919, 2.396] 0.107/ 1.137 [0.947, 1.365] 0.168/ 0.082 [-0.030, 0.194] 0.152

Produced: 17 December 2020

Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15b Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	212	244	103		
Effect					
Treatment				0.908	
Baseline				0.002	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.088 [0.743, 1.591] 0.666/ 1.016 [0.879, 1.173] 0.832/ 0.020 [-0.070, 0.109] 0.669
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.029 [0.633, 1.674] 0.908/ 1.012 [0.840, 1.220] 0.898/ 0.016 [-0.099, 0.131] 0.785
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.057 [0.657, 1.699] 0.820/ 1.003 [0.834, 1.207] 0.971/ 0.004 [-0.109, 0.116] 0.950

Produced: 17 December 2020

Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15b Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value
Gender: Female					
Visit 5 (Week 26)					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.976	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.998 [0.723, 1.376] 0.990/0.999 [0.946, 1.056] 0.984/0.022 [-0.050, 0.095] 0.543
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.039 [0.711, 1.519] 0.844/1.005 [0.943, 1.071] 0.882/0.027 [-0.059, 0.113] 0.542
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.960 [0.654, 1.411] 0.837/0.995 [0.931, 1.062] 0.872/-0.004 [-0.092, 0.083] 0.924

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15b Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Gender (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	359	327	184		
Effect					
Treatment				0.686	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.096 [0.797, 1.505] 0.574/ 1.016 [0.932, 1.108] 0.712/ 0.037 [-0.035, 0.109] 0.319
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.173 [0.807, 1.704] 0.404/ 1.036 [0.934, 1.149] 0.503/ 0.049 [-0.037, 0.135] 0.267
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.934 [0.641, 1.362] 0.724/ 0.981 [0.881, 1.092] 0.727/ -0.012 [-0.100, 0.076] 0.787

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.404	
Visit Period				0.036*	
Treatment*Visit Period				0.328	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.646	-0.562	-0.641		
[95% CI]	[-0.761, -0.530]	[-0.672, -0.451]	[-0.806, -0.476]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.084 [-0.244, 0.076] 0.301
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.005 [-0.206, 0.197] 0.963
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.079 [-0.278, 0.120] 0.433

Produced: 17 December 2020 Page 1 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.764	-0.684	-0.858		
[95% CI]	[-0.892, -0.635]	[-0.807, -0.561]	[-1.042, -0.674]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.080 [-0.258, 0.098] 0.379
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.094 [-0.130, 0.319] 0.409
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.174 [-0.396, 0.047] 0.123
Visit 5 (Week 26)					
Adjusted Mean	-0.833	-0.791	-0.871		
[95% CI]	[-0.968, -0.698]	[-0.919, -0.662]	[-1.064, -0.677]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.228, 0.144] 0.659
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [-0.198, 0.274] 0.753
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.080 [-0.312, 0.153] 0.500

Produced: 17 December 2020

Page 2 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.860	-0.801	-0.934		
[95% CI]	[-0.993, -0.728]	[-0.927, -0.676]	[-1.125, -0.744]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.059 [-0.242, 0.123] 0.525
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.074 [-0.158, 0.306] 0.530
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.133 [-0.361, 0.095] 0.252
Visit 7 (Week 52)					
Adjusted Mean	-1.022	-0.842	-0.870		
[95% CI]	[-1.158, -0.886]	[-0.971, -0.713]	[-1.068, -0.672]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.180 [-0.368, 0.008] 0.060
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.152 [-0.393, 0.089] 0.215
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.264, 0.209] 0.816

Produced: 17 December 2020

Page 3 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.859	-0.771	-0.868		
[95% CI]	[-0.971, -0.746]	[-0.878, -0.664]	[-1.030, -0.706]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.087 [-0.243, 0.068] 0.269
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.009 [-0.188, 0.206] 0.926
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.097 [-0.291, 0.097] 0.327

Produced: 17 December 2020 Page 4 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: [25-30)					
Number of Patients Included in Model	216	200	110		
Effect					
Treatment				0.536	
Visit Period				0.193	
Treatment*Visit Period				0.263	
Baseline				<0.001***	
Baseline*Visit Period				0.003**	
Visit 3 (Week 4)					
Adjusted Mean	-0.647	-0.576	-0.597		
[95% CI]	[-0.740, -0.554]	[-0.673, -0.479]	[-0.728, -0.467]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.071 [-0.206, 0.063] 0.298
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.050 [-0.210, 0.110] 0.541
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.021 [-0.184, 0.141] 0.797

Produced: 17 December 2020 Page 5 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.759	-0.712	-0.751		
[95% CI]	[-0.860, -0.657]	[-0.818, -0.607]	[-0.895, -0.608]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.193, 0.100] 0.531
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.007 [-0.183, 0.168] 0.934
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.039 [-0.217, 0.139] 0.665
Visit 5 (Week 26)					
Adjusted Mean	-0.886	-0.793	-0.877		
[95% CI]	[-0.994, -0.777]	[-0.907, -0.680]	[-1.031, -0.724]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.092 [-0.249, 0.065] 0.249
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.008 [-0.196, 0.180] 0.933
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.084 [-0.275, 0.107] 0.387

Produced: 17 December 2020

Page 6 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.894	-0.875	-0.746		
[95% CI]	[-1.006, -0.783]	[-0.992, -0.759]	[-0.904, -0.587]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.019 [-0.180, 0.143] 0.820
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.149 [-0.342, 0.045] 0.132
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.130 [-0.067, 0.326] 0.195
Visit 7 (Week 52)					
Adjusted Mean	-0.950	-0.852	-0.828		
[95% CI]	[-1.063, -0.837]	[-0.971, -0.734]	[-0.989, -0.666]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.098 [-0.262, 0.067] 0.244
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.122 [-0.320, 0.075] 0.225
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.025 [-0.176, 0.225] 0.810

Produced: 17 December 2020

Page 7 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.865	-0.800	-0.790		
[95% CI]	[-0.958, -0.772]	[-0.897, -0.703]	[-0.922, -0.657]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.065 [-0.200, 0.070] 0.344
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.075 [-0.237, 0.087] 0.361
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.010 [-0.154, 0.174] 0.902

Produced: 17 December 2020 Page 8 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	203	202	102		
Effect					
Treatment				0.449	
Visit Period				0.617	
Treatment*Visit Period				0.805	
Baseline				<0.001***	
Baseline*Visit Period				0.007**	
Visit 3 (Week 4)					
Adjusted Mean	-0.553	-0.545	-0.589		
[95% CI]	[-0.651, -0.454]	[-0.644, -0.447]	[-0.728, -0.450]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.008 [-0.147, 0.132] 0.914
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.036 [-0.134, 0.207] 0.676
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-0.214, 0.126] 0.612

Produced: 17 December 2020 Page 9 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.725	-0.646	-0.690		
[95% CI]	[-0.826, -0.624]	[-0.748, -0.545]	[-0.832, -0.548]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.079 [-0.222, 0.065] 0.282
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.035 [-0.209, 0.140] 0.698
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.044 [-0.218, 0.130] 0.620
Visit 5 (Week 26)					
Adjusted Mean	-0.818	-0.732	-0.742		
[95% CI]	[-0.927, -0.710]	[-0.841, -0.624]	[-0.894, -0.590]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.240, 0.068] 0.272
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.076 [-0.263, 0.111] 0.426
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.010 [-0.197, 0.176] 0.915

Produced: 17 December 2020 Page 10 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.838	-0.708	-0.834		
[95% CI]	[-0.954, -0.723]	[-0.823, -0.593]	[-0.996, -0.673]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.130 [-0.293, 0.033] 0.118
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.004 [-0.203, 0.195] 0.968
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.126 [-0.324, 0.072] 0.211
Visit 7 (Week 52)					
Adjusted Mean	-0.840	-0.751	-0.845		
[95% CI]	[-0.958, -0.723]	[-0.868, -0.634]	[-1.008, -0.681]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.089 [-0.255, 0.077] 0.290
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.004 [-0.198, 0.206] 0.967
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.094 [-0.295, 0.107] 0.360

Produced: 17 December 2020 Page 11 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12c Statistical Analysis of ACQ-5 total score by Bmi
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.794	-0.702	-0.771		
[95% CI]	[-0.888, -0.700]	[-0.796, -0.609]	[-0.902, -0.640]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.092 [-0.224, 0.041] 0.176
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.023 [-0.185, 0.139] 0.780
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.068 [-0.230, 0.093] 0.404

Produced: 17 December 2020 Page 12 of 12

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13c ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
BMI Class: < 25	(N=150)	(N=163)	(N=73)
Visit 5 (Week 26)			
Responders	94 (16.5)	96 (16.8)	49 (17.1)
Non-Responders	56 (9.8)	67 (11.7)	24 (8.4)
Change > -0.5	56 (9.8)	67 (11.7)	24 (8.4)
Visit 7 (Week 52)			
Responders	100 (17.5)	100 (17.5)	42 (14.6)
Non-Responders	50 (8.8)	63 (11.0)	31 (10.8)
Change > -0.5	49 (8.6)	63 (11.0)	31 (10.8)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 1 of 3

Source: Not Applicable

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
 [2] Table presents number and percentage of patients (n (%))
 [3] Percentages are based on the number of patients in the relevant treatment/population (N)
 [4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13c ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
BMI Class: [25-30)	(N=217)	(N=205)	(N=112)
Visit 5 (Week 26)			
Responders	145 (25.4)	122 (21.4)	68 (23.7)
Non-Responders	72 (12.6)	83 (14.5)	44 (15.3)
Change > -0.5	71 (12.4)	82 (14.4)	44 (15.3)
Missing data	1 (0.2)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	143 (25.0)	121 (21.2)	63 (22.0)
Non-Responders	74 (13.0)	84 (14.7)	49 (17.1)
Change > -0.5	74 (13.0)	84 (14.7)	49 (17.1)

Produced: 17 December 2020

Page 2 of 3

Source: Not Applicable

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
 [2] Table presents number and percentage of patients (n (%))
 [3] Percentages are based on the number of patients in the relevant treatment/population (N)
 [4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13c ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
BMI Class: >=30	(N=204)	(N=203)	(N=102)
Visit 5 (Week 26)			
Responders	128 (22.4)	120 (21.0)	62 (21.6)
Non-Responders	76 (13.3)	83 (14.5)	40 (13.9)
Change > -0.5	75 (13.1)	83 (14.5)	40 (13.9)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	124 (21.7)	128 (22.4)	69 (24.0)
Non-Responders	80 (14.0)	75 (13.1)	33 (11.5)
Change > -0.5	80 (14.0)	75 (13.1)	33 (11.5)

Produced: 17 December 2020

Page 3 of 3

Source: Not Applicable

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
 [2] Table presents number and percentage of patients (n (%))
 [3] Percentages are based on the number of patients in the relevant treatment/population (N)
 [4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
BMI Class: < 25					
Visit 5 (Week 26)					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.379	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.160 [0.727, 1.851] 0.535/ 1.018 [0.926, 1.119] 0.717/ 0.030 [-0.078, 0.138] 0.585
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.759 [0.414, 1.394] 0.374/ 0.969 [0.863, 1.088] 0.595/ -0.045 [-0.179, 0.089] 0.507
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.527 [0.840, 2.776] 0.165/ 1.050 [0.935, 1.180] 0.410/ 0.075 [-0.059, 0.209] 0.270

Produced: 17 December 2020

Page 1 of 6

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	150	163	73		
Effect Treatment Baseline				0.461 <0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.250 [0.778, 2.009] 0.356/ 1.026 [0.933, 1.128] 0.598/ 0.043 [-0.064, 0.150] 0.433
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.414 [0.783, 2.550] 0.250/ 1.045 [0.921, 1.185] 0.493/ 0.067 [-0.070, 0.205] 0.339
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.884 [0.497, 1.575] 0.677/ 0.982 [0.865, 1.114] 0.774/ -0.024 [-0.162, 0.114] 0.730

Produced: 17 December 2020

Page 2 of 6

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
BMI Class: [25-30)					
Visit 5 (Week 26)					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.359	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.315 [0.879, 1.967] 0.182/ 1.090 [0.946, 1.256] 0.234/ 0.060 [-0.031, 0.151] 0.193
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.289 [0.799, 2.080] 0.299/ 1.093 [0.920, 1.297] 0.312/ 0.056 [-0.052, 0.163] 0.308
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.020 [0.633, 1.644] 0.934/ 0.998 [0.831, 1.197] 0.979/ 0.004 [-0.106, 0.115] 0.938

Produced: 17 December 2020

Page 3 of 6

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.208	
Baseline				0.002	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.294 [0.868, 1.929] 0.207/ 1.071 [0.923, 1.243] 0.364/ 0.053 [-0.039, 0.146] 0.259
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.491 [0.931, 2.389] 0.097/ 1.165 [0.968, 1.403] 0.107/ 0.091 [-0.018, 0.200] 0.100
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.868 [0.542, 1.389] 0.554/ 0.919 [0.755, 1.120] 0.404/ -0.038 [-0.151, 0.074] 0.507

Produced: 17 December 2020

Page 4 of 6

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
- [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
- [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
BMI Class: >=30					
Visit 5 (Week 26)					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.879	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.081 [0.717, 1.630] 0.709/ 1.016 [0.885, 1.167] 0.821/ 0.014 [-0.078, 0.105] 0.770
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.960 [0.581, 1.588] 0.875/ 0.994 [0.840, 1.176] 0.943/ -0.008 [-0.118, 0.103] 0.891
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.126 [0.683, 1.857] 0.641/ 1.022 [0.860, 1.215] 0.801/ 0.021 [-0.090, 0.133] 0.707

Produced: 17 December 2020

Page 5 of 6

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15c Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by BMI Class (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	204	203	102		
Effect					
Treatment				0.343	
Baseline				0.002	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.865 [0.577, 1.298] 0.484/ 0.953 [0.821, 1.106] 0.523/ -0.031 [-0.125, 0.062] 0.510
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.685 [0.412, 1.139] 0.145/ 0.883 [0.746, 1.044] 0.145/ -0.083 [-0.194, 0.028] 0.143
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.262 [0.759, 2.099] 0.369/ 1.079 [0.916, 1.272] 0.363/ 0.052 [-0.059, 0.162] 0.359

Produced: 17 December 2020

Page 6 of 6

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	486	486	243		
Effect					
Treatment				0.245	
Visit Period				0.139	
Treatment*Visit Period				0.900	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.628	-0.583	-0.606		
[95% CI]	[-0.691, -0.565]	[-0.646, -0.520]	[-0.695, -0.516]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.045 [-0.134, 0.044] 0.322
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.022 [-0.132, 0.087] 0.688
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.132, 0.086] 0.684

Produced: 17 December 2020

Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.761	-0.711	-0.781		
[95% CI]	[-0.828, -0.694]	[-0.778, -0.644]	[-0.876, -0.687]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.050 [-0.145, 0.044] 0.296
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.020 [-0.096, 0.136] 0.734
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.071 [-0.186, 0.045] 0.233
Visit 5 (Week 26)					
Adjusted Mean	-0.877	-0.807	-0.857		
[95% CI]	[-0.948, -0.805]	[-0.879, -0.736]	[-0.958, -0.756]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.069 [-0.170, 0.032] 0.180
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.019 [-0.143, 0.105] 0.758
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.050 [-0.174, 0.074] 0.430

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.902	-0.821	-0.857		
[95% CI]	[-0.976, -0.829]	[-0.895, -0.748]	[-0.961, -0.753]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.081 [-0.185, 0.023] 0.126
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.045 [-0.173, 0.083] 0.489
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.036 [-0.164, 0.091] 0.579
Visit 7 (Week 52)					
Adjusted Mean	-0.962	-0.858	-0.891		
[95% CI]	[-1.038, -0.887]	[-0.933, -0.784]	[-0.998, -0.784]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.104 [-0.210, 0.002] 0.055
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.071 [-0.202, 0.059] 0.283
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.033 [-0.163, 0.098] 0.624

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.866	-0.791	-0.834		
[95% CI]	[-0.927, -0.805]	[-0.852, -0.730]	[-0.920, -0.748]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.076 [-0.162, 0.011] 0.085
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.032 [-0.138, 0.073] 0.547
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.043 [-0.149, 0.062] 0.422

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	79	42		
Effect					
Treatment				0.550	
Visit Period				0.035*	
Treatment*Visit Period				0.566	
Baseline				<0.001***	
Baseline*Visit Period				0.004**	
Visit 3 (Week 4)					
Adjusted Mean	-0.525	-0.421	-0.612		
[95% CI]	[-0.679, -0.371]	[-0.579, -0.264]	[-0.828, -0.397]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.104 [-0.324, 0.117] 0.354
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.087 [-0.178, 0.353] 0.518
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.191 [-0.458, 0.076] 0.160

Produced: 17 December 2020

Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.668	-0.498	-0.619		
[95% CI]	[-0.844, -0.492]	[-0.677, -0.318]	[-0.866, -0.371]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.170 [-0.422, 0.081] 0.184
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.049 [-0.353, 0.255] 0.752
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.121 [-0.427, 0.184] 0.434
Visit 5 (Week 26)					
Adjusted Mean	-0.669	-0.551	-0.645		
[95% CI]	[-0.851, -0.487]	[-0.737, -0.365]	[-0.905, -0.386]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.117 [-0.378, 0.143] 0.375
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.341, 0.294] 0.884
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.094 [-0.413, 0.225] 0.563

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.633	-0.634	-0.633		
[95% CI]	[-0.819, -0.447]	[-0.823, -0.446]	[-0.897, -0.370]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.001 [-0.264, 0.266] 0.992
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.000 [-0.323, 0.323] 0.999
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.001 [-0.323, 0.325] 0.995
Visit 7 (Week 52)					
Adjusted Mean	-0.718	-0.532	-0.577		
[95% CI]	[-0.907, -0.528]	[-0.724, -0.340]	[-0.846, -0.308]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.186 [-0.456, 0.085] 0.177
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.141 [-0.470, 0.189] 0.401
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.045 [-0.375, 0.285] 0.788

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12d Statistical Analysis of ACQ-5 total score by Smoking Status
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.659	-0.551	-0.620		
[95% CI]	[-0.816, -0.503]	[-0.711, -0.392]	[-0.841, -0.398]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.108 [-0.332, 0.116] 0.341
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.040 [-0.311, 0.232] 0.775
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.069 [-0.341, 0.204] 0.620

Produced: 17 December 2020

Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13d ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Smoking Status
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Smoking Status: Non smoker	(N=488)	(N=491)	(N=245)
Visit 5 (Week 26)			
Responders	319 (55.9)	302 (52.9)	158 (55.1)
Non-Responders	169 (29.6)	189 (33.1)	87 (30.3)
Change > -0.5	168 (29.4)	188 (32.9)	87 (30.3)
Missing data	1 (0.2)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	323 (56.6)	311 (54.5)	155 (54.0)
Non-Responders	165 (28.9)	180 (31.5)	90 (31.4)
Change > -0.5	164 (28.7)	180 (31.5)	90 (31.4)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13d ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Smoking Status
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Smoking Status: Ex-smoker	(N=83)	(N=80)	(N=42)
Visit 5 (Week 26)			
Responders	48 (8.4)	36 (6.3)	21 (7.3)
Non-Responders	35 (6.1)	44 (7.7)	21 (7.3)
Change > -0.5	34 (6.0)	44 (7.7)	21 (7.3)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	44 (7.7)	38 (6.7)	19 (6.6)
Non-Responders	39 (6.8)	42 (7.4)	23 (8.0)
Change > -0.5	39 (6.8)	42 (7.4)	23 (8.0)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Table presents number and percentage of patients (n (%))
 [3] Percentages are based on the number of patients in the relevant treatment/population (N)
 [4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15d Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Smoking Status: Non smoker					
Visit 5 (Week 26)					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.559	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.134 [0.869, 1.480] 0.353/ 1.025 [0.956, 1.098] 0.491/ 0.026 [-0.032, 0.084] 0.383
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.981 [0.707, 1.362] 0.910/ 0.999 [0.919, 1.087] 0.983/ -0.004 [-0.074, 0.067] 0.922
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.156 [0.835, 1.600] 0.383/ 1.026 [0.942, 1.117] 0.563/ 0.030 [-0.042, 0.101] 0.417

Produced: 17 December 2020

Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15d Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	488	491	245		
Effect					
Treatment				0.759	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.098 [0.842, 1.432] 0.490/ 1.022 [0.934, 1.118] 0.633/ 0.018 [-0.041, 0.077] 0.554
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.093 [0.790, 1.511] 0.592/ 1.030 [0.921, 1.151] 0.605/ 0.019 [-0.053, 0.092] 0.601
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.005 [0.729, 1.386] 0.976/ 0.992 [0.886, 1.112] 0.896/ -0.001 [-0.074, 0.071] 0.969

Produced: 17 December 2020

Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15d Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Smoking Status: Ex-smoker					
Visit 5 (Week 26)					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.372	
Baseline				0.002	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.579 [0.835, 2.984] 0.160/ 1.163 [0.882, 1.534] 0.285/ 0.104 [-0.047, 0.256] 0.176
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.267 [0.591, 2.718] 0.543/ 1.082 [0.787, 1.488] 0.626/ 0.041 [-0.137, 0.220] 0.651
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.246 [0.579, 2.683] 0.574/ 1.075 [0.762, 1.515] 0.682/ 0.063 [-0.117, 0.244] 0.493

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15d Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Smoking Status (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.798	
Baseline				0.006	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.168 [0.622, 2.191] 0.629/ 1.040 [0.785, 1.378] 0.785/ 0.033 [-0.120, 0.185] 0.675
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.273 [0.596, 2.719] 0.534/ 1.084 [0.766, 1.535] 0.649/ 0.048 [-0.133, 0.229] 0.601
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.917 [0.427, 1.969] 0.825/ 0.959 [0.671, 1.372] 0.820/ -0.016 [-0.199, 0.167] 0.867

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	437	445	227		
Effect					
Treatment				0.206	
Visit Period				0.024*	
Treatment*Visit Period				0.578	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.615	-0.587	-0.593		
[95% CI]	[-0.681, -0.549]	[-0.652, -0.522]	[-0.684, -0.501]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.027 [-0.120, 0.065] 0.562
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.022 [-0.135, 0.091] 0.703
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.118, 0.107] 0.924

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.742	-0.678	-0.743		
[95% CI]	[-0.812, -0.671]	[-0.748, -0.608]	[-0.841, -0.644]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.064 [-0.164, 0.036] 0.208
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.120, 0.122] 0.986
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.065 [-0.186, 0.056] 0.290
Visit 5 (Week 26)					
Adjusted Mean	-0.847	-0.772	-0.775		
[95% CI]	[-0.923, -0.772]	[-0.847, -0.698]	[-0.880, -0.670]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.075 [-0.181, 0.031] 0.167
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.072 [-0.201, 0.058] 0.277
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.003 [-0.132, 0.126] 0.963

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.870	-0.773	-0.799		
[95% CI]	[-0.946, -0.793]	[-0.849, -0.697]	[-0.906, -0.692]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.097 [-0.205, 0.011] 0.080
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.071 [-0.203, 0.061] 0.293
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.026 [-0.157, 0.105] 0.700
Visit 7 (Week 52)					
Adjusted Mean	-0.917	-0.794	-0.800		
[95% CI]	[-0.996, -0.838]	[-0.872, -0.715]	[-0.911, -0.690]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.124 [-0.235, -0.012] 0.030*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.117 [-0.253, 0.019] 0.092
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.007 [-0.142, 0.129] 0.924

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.835	-0.749	-0.768		
[95% CI]	[-0.900, -0.771]	[-0.813, -0.685]	[-0.858, -0.678]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.087 [-0.178, 0.004] 0.062
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.067 [-0.178, 0.044] 0.237
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.130, 0.091] 0.726

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.331	
Visit Period				0.257	
Treatment*Visit Period				0.650	
Baseline				<0.001***	
Baseline*Visit Period				0.006**	
Visit 3 (Week 4)					
Adjusted Mean	-0.609	-0.460	-0.658		
[95% CI]	[-0.733, -0.485]	[-0.591, -0.330]	[-0.846, -0.471]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.149 [-0.329, 0.032] 0.106
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.049 [-0.176, 0.275] 0.666
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.198 [-0.427, 0.031] 0.089

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.766	-0.693	-0.821		
[95% CI]	[-0.902, -0.630]	[-0.835, -0.551]	[-1.026, -0.615]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.270, 0.124] 0.465
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.054 [-0.192, 0.301] 0.664
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.127 [-0.377, 0.122] 0.316
Visit 5 (Week 26)					
Adjusted Mean	-0.843	-0.771	-1.034		
[95% CI]	[-0.986, -0.699]	[-0.921, -0.621]	[-1.250, -0.819]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.072 [-0.279, 0.136] 0.496
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.192 [-0.067, 0.451] 0.146
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.264 [-0.526, -0.001] 0.049*

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.851	-0.873	-0.928		
[95% CI]	[-1.004, -0.699]	[-1.032, -0.714]	[-1.157, -0.699]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.022 [-0.198, 0.242] 0.845
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.076 [-0.199, 0.352] 0.586
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.054 [-0.333, 0.225] 0.702
Visit 7 (Week 52)					
Adjusted Mean	-0.965	-0.882	-1.026		
[95% CI]	[-1.116, -0.814]	[-1.040, -0.725]	[-1.256, -0.797]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.083 [-0.301, 0.135] 0.455
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.061 [-0.214, 0.336] 0.661
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.144 [-0.423, 0.134] 0.309

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12e Statistical Analysis of ACQ-5 total score by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.843	-0.788	-0.942		
[95% CI]	[-0.965, -0.722]	[-0.916, -0.661]	[-1.126, -0.758]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.055 [-0.231, 0.121] 0.538
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.099 [-0.122, 0.319] 0.380
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.154 [-0.377, 0.070] 0.177

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13e ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Number of Exacerbation in the Previous year: 1	(N=439)	(N=451)	(N=229)
Visit 5 (Week 26)			
Responders	282 (49.4)	263 (46.1)	137 (47.7)
Non-Responders	157 (27.5)	188 (32.9)	92 (32.1)
Change > -0.5	157 (27.5)	187 (32.7)	92 (32.1)
Missing data	0 (0.0)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	285 (49.9)	268 (46.9)	138 (48.1)
Non-Responders	154 (27.0)	183 (32.0)	91 (31.7)
Change > -0.5	153 (26.8)	183 (32.0)	91 (31.7)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13e ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Number of Exacerbation in the Previous year: > 1	(N=132)	(N=120)	(N=58)
Visit 5 (Week 26)			
Responders	85 (14.9)	75 (13.1)	42 (14.6)
Non-Responders	47 (8.2)	45 (7.9)	16 (5.6)
Change > -0.5	45 (7.9)	45 (7.9)	16 (5.6)
Missing data	2 (0.4)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	82 (14.4)	81 (14.2)	36 (12.5)
Non-Responders	50 (8.8)	39 (6.8)	22 (7.7)
Change > -0.5	50 (8.8)	39 (6.8)	22 (7.7)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15e Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Visit 5 (Week 26)					
Number of Patients Included in Model	439	451	229		
Effect Treatment Baseline				0.399 <0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.212 [0.918, 1.599] 0.175/1.022 [0.965, 1.083] 0.460/0.037 [-0.028, 0.102] 0.261
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.106 [0.790, 1.549] 0.556/1.013 [0.945, 1.086] 0.713/0.019 [-0.059, 0.096] 0.635
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.095 [0.786, 1.526] 0.591/1.009 [0.940, 1.082] 0.807/0.018 [-0.059, 0.096] 0.645

Produced: 17 December 2020

Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15e Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Number of Exacerbation in the Previous year (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	439	451	229		
Effect Treatment Baseline				0.393	<0.001***
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.209 [0.917, 1.592] 0.178/ 1.052 [0.951, 1.163] 0.324/ 0.038 [-0.025, 0.101] 0.235
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.145 [0.819, 1.598] 0.428/ 1.038 [0.917, 1.175] 0.551/ 0.027 [-0.050, 0.103] 0.496
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.056 [0.760, 1.467] 0.746/ 1.013 [0.892, 1.150] 0.844/ 0.012 [-0.066, 0.089] 0.770

Produced: 17 December 2020 Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15e Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Visit 5 (Week 26)					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.456	
Baseline				0.008	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.081 [0.643, 1.817] 0.770/ 1.027 [0.856, 1.232] 0.775/ 0.019 [-0.098, 0.137] 0.749
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.698 [0.352, 1.385] 0.304/ 0.917 [0.752, 1.119] 0.394/ -0.067 [-0.204, 0.070] 0.337
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.548 [0.774, 3.095] 0.216/ 1.120 [0.916, 1.369] 0.270/ 0.086 [-0.053, 0.226] 0.225

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15e Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Number of Exacerbation in the Previous year
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	132	120	58		
Effect					
Treatment				0.591	
Baseline				0.013	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.781 [0.462, 1.321] 0.357/ 0.917 [0.768, 1.093] 0.333/ -0.056 [-0.172, 0.060] 0.346
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.025 [0.538, 1.951] 0.940/ 1.018 [0.805, 1.289] 0.880/ 0.009 [-0.138, 0.156] 0.908
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.762 [0.393, 1.478] 0.422/ 0.900 [0.717, 1.129] 0.362/ -0.065 [-0.212, 0.083] 0.390

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	298	275	146		
Effect					
Treatment				0.161	
Visit Period				0.045*	
Treatment*Visit Period				0.749	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.599	-0.532	-0.541		
[95% CI]	[-0.678, -0.519]	[-0.615, -0.449]	[-0.655, -0.427]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.067 [-0.182, 0.049] 0.257
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.058 [-0.197, 0.081] 0.416
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.150, 0.132] 0.902

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.749	-0.664	-0.698		
[95% CI]	[-0.838, -0.660]	[-0.756, -0.572]	[-0.826, -0.571]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.085 [-0.214, 0.043] 0.193
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.051 [-0.207, 0.104] 0.518
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.034 [-0.191, 0.123] 0.671
Visit 5 (Week 26)					
Adjusted Mean	-0.824	-0.732	-0.763		
[95% CI]	[-0.919, -0.729]	[-0.830, -0.633]	[-0.899, -0.626]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.093 [-0.230, 0.044] 0.184
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.062 [-0.228, 0.105] 0.467
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.031 [-0.199, 0.137] 0.717

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.856	-0.764	-0.738		
[95% CI]	[-0.954, -0.758]	[-0.866, -0.663]	[-0.879, -0.597]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.092 [-0.233, 0.050] 0.205
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.118 [-0.290, 0.054] 0.180
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.026 [-0.148, 0.200] 0.766
Visit 7 (Week 52)					
Adjusted Mean	-0.919	-0.771	-0.724		
[95% CI]	[-1.017, -0.821]	[-0.872, -0.669]	[-0.865, -0.583]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.148 [-0.289, -0.007] 0.040*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.195 [-0.367, -0.023] 0.026*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.047 [-0.126, 0.221] 0.594

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.826	-0.724	-0.720		
[95% CI]	[-0.906, -0.746]	[-0.807, -0.641]	[-0.835, -0.605]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.102 [-0.218, 0.014] 0.084
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.106 [-0.246, 0.034] 0.139
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.004 [-0.138, 0.145] 0.959

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	270	290	139		
Effect					
Treatment				0.283	
Visit Period				0.330	
Treatment*Visit Period				0.994	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.629	-0.588	-0.676		
[95% CI]	[-0.715, -0.544]	[-0.671, -0.506]	[-0.796, -0.557]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.041 [-0.160, 0.078] 0.498
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.100, 0.194] 0.528
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.088 [-0.233, 0.057] 0.232

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.746	-0.698	-0.820		
[95% CI]	[-0.834, -0.657]	[-0.783, -0.613]	[-0.943, -0.697]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.047 [-0.170, 0.075] 0.449
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.075 [-0.077, 0.226] 0.332
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.122 [-0.272, 0.027] 0.109
Visit 5 (Week 26)					
Adjusted Mean	-0.874	-0.812	-0.895		
[95% CI]	[-0.968, -0.781]	[-0.902, -0.721]	[-1.026, -0.765]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.062 [-0.192, 0.068] 0.347
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.021 [-0.140, 0.182] 0.797
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.083 [-0.242, 0.075] 0.303

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.874	-0.825	-0.920		
[95% CI]	[-0.970, -0.779]	[-0.917, -0.733]	[-1.053, -0.787]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.049 [-0.182, 0.083] 0.465
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.045 [-0.118, 0.209] 0.587
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.095 [-0.256, 0.067] 0.250
Visit 7 (Week 52)					
Adjusted Mean	-0.938	-0.855	-0.976		
[95% CI]	[-1.038, -0.837]	[-0.951, -0.758]	[-1.116, -0.836]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.083 [-0.222, 0.057] 0.244
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.039 [-0.133, 0.211] 0.659
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.121 [-0.291, 0.049] 0.161

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12f Statistical Analysis of ACQ-5 total score by Degree of reversibility at screening (delta FEV1)
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.850	-0.791	-0.892		
[95% CI]	[-0.931, -0.769]	[-0.869, -0.712]	[-1.005, -0.779]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.172, 0.053] 0.300
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.042 [-0.097, 0.181] 0.554
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.102 [-0.239, 0.036] 0.148

Produced: 17 December 2020

Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13f ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Degree of reversibility at screening (delta FEV1)
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Degree of reversibility at screening (delta FEV1): (200-400] (N=299) mL		(N=281)	(N=147)
Visit 5 (Week 26)			
Responders	181 (31.7)	153 (26.8)	81 (28.2)
Non-Responders	118 (20.7)	128 (22.4)	66 (23.0)
Change > -0.5	117 (20.5)	128 (22.4)	66 (23.0)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	186 (32.6)	161 (28.2)	80 (27.9)
Non-Responders	113 (19.8)	120 (21.0)	67 (23.3)
Change > -0.5	113 (19.8)	120 (21.0)	67 (23.3)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13f ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Degree of reversibility at screening (delta FEV1)
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Degree of reversibility at screening (delta FEV1): > 400 mL (N=271)		(N=290)	(N=140)
Visit 5 (Week 26)			
Responders	186 (32.6)	185 (32.4)	98 (34.1)
Non-Responders	85 (14.9)	105 (18.4)	42 (14.6)
Change > -0.5	84 (14.7)	104 (18.2)	42 (14.6)
Missing data	1 (0.2)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	181 (31.7)	188 (32.9)	94 (32.8)
Non-Responders	90 (15.8)	102 (17.9)	46 (16.0)
Change > -0.5	89 (15.6)	102 (17.9)	46 (16.0)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15f Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Visit 5 (Week 26)					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.505	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.210 [0.863, 1.695] 0.268/
					1.032 [0.938, 1.135] 0.521/
					0.036 [-0.044, 0.116] 0.382
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.180 [0.785, 1.773] 0.426/
					1.034 [0.925, 1.156] 0.557/
					0.033 [-0.061, 0.128] 0.488
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.025 [0.681, 1.544] 0.905/
					0.998 [0.887, 1.122] 0.970/
					0.002 [-0.095, 0.100] 0.963

Produced: 17 December 2020 Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15f Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	299	281	147		
Effect					
Treatment				0.367	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.173 [0.837, 1.642] 0.354/ 1.041 [0.912, 1.188] 0.552/ 0.033 [-0.046, 0.113] 0.412
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.323 [0.883, 1.983] 0.174/ 1.124 [0.949, 1.330] 0.176/ 0.065 [-0.030, 0.161] 0.179
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.886 [0.590, 1.330] 0.559/ 0.926 [0.777, 1.104] 0.394/ -0.032 [-0.130, 0.066] 0.519

Produced: 17 December 2020 Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15f Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Visit 5 (Week 26)					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.318	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.208 [0.843, 1.730] 0.303/ 1.027 [0.956, 1.104] 0.460/ 0.038 [-0.041, 0.117] 0.349
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.876 [0.557, 1.379] 0.568/ 0.986 [0.904, 1.076] 0.755/ -0.021 [-0.117, 0.076] 0.671
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.378 [0.884, 2.148] 0.156/ 1.042 [0.955, 1.136] 0.354/ 0.059 [-0.037, 0.154] 0.229

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15f Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Degree of reversibility at screening (delta FEV1) (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.842	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.062 [0.745, 1.514] 0.739/ 1.012 [0.908, 1.129] 0.826/ 0.010 [-0.066, 0.086] 0.796
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.936 [0.602, 1.454] 0.767/ 0.971 [0.848, 1.112] 0.671/ -0.022 [-0.116, 0.073] 0.656
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.135 [0.736, 1.751] 0.566/ 1.042 [0.911, 1.193] 0.547/ 0.032 [-0.063, 0.126] 0.511

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	128	137	74		
Effect					
Treatment				0.651	
Visit Period				0.178	
Treatment*Visit Period				0.496	
Baseline				<0.001***	
Baseline*Visit Period				0.006**	
Visit 3 (Week 4)					
Adjusted Mean	-0.657	-0.659	-0.776		
[95% CI]	[-0.793, -0.521]	[-0.790, -0.528]	[-0.955, -0.596]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.002 [-0.187, 0.191] 0.984
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.118 [-0.107, 0.343] 0.302
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.116 [-0.339, 0.106] 0.303

Produced: 17 December 2020

Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.803	-0.779	-0.906		
[95% CI]	[-0.939, -0.668]	[-0.909, -0.648]	[-1.085, -0.727]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.213, 0.163] 0.794
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.103 [-0.122, 0.327] 0.369
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.127 [-0.349, 0.094] 0.259
Visit 5 (Week 26)					
Adjusted Mean	-0.882	-0.893	-0.886		
[95% CI]	[-1.026, -0.739]	[-1.032, -0.754]	[-1.076, -0.696]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					0.010 [-0.189, 0.210] 0.918
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.003 [-0.235, 0.242] 0.977
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.007 [-0.229, 0.243] 0.954

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-1.015	-0.880	-0.976		
[95% CI]	[-1.163, -0.867]	[-1.024, -0.736]	[-1.172, -0.780]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.135 [-0.341, 0.071] 0.200
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.039 [-0.284, 0.207] 0.758
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.096 [-0.340, 0.147] 0.438
Visit 7 (Week 52)					
Adjusted Mean	-0.985	-0.850	-0.945		
[95% CI]	[-1.133, -0.836]	[-0.994, -0.706]	[-1.142, -0.748]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.135 [-0.342, 0.072] 0.200
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.039 [-0.287, 0.208] 0.754
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.096 [-0.340, 0.149] 0.442

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.912	-0.844	-0.919		
[95% CI]	[-1.036, -0.788]	[-0.964, -0.724]	[-1.082, -0.755]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.068 [-0.241, 0.104] 0.436
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.006 [-0.199, 0.212] 0.951
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.075 [-0.278, 0.129] 0.471

Produced: 17 December 2020 Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	441	428	211		
Effect					
Treatment				0.160	
Visit Period				0.039*	
Treatment*Visit Period				0.845	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.600	-0.527	-0.551		
[95% CI]	[-0.664, -0.536]	[-0.592, -0.462]	[-0.643, -0.458]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.073 [-0.164, 0.018] 0.115
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.050 [-0.162, 0.062] 0.385
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.136, 0.089] 0.682

Produced: 17 December 2020

Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.731	-0.649	-0.707		
[95% CI]	[-0.802, -0.660]	[-0.720, -0.577]	[-0.809, -0.605]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.082 [-0.183, 0.018] 0.109
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.024 [-0.148, 0.100] 0.704
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.058 [-0.183, 0.066] 0.360
Visit 5 (Week 26)					
Adjusted Mean	-0.836	-0.734	-0.807		
[95% CI]	[-0.911, -0.760]	[-0.810, -0.657]	[-0.916, -0.697]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.102 [-0.209, 0.005] 0.063
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.029 [-0.162, 0.104] 0.667
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.073 [-0.206, 0.060] 0.283

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.819	-0.765	-0.776		
[95% CI]	[-0.896, -0.742]	[-0.843, -0.687]	[-0.888, -0.664]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.054 [-0.164, 0.056] 0.338
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.043 [-0.179, 0.093] 0.538
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.011 [-0.147, 0.125] 0.874
Visit 7 (Week 52)					
Adjusted Mean	-0.911	-0.800	-0.816		
[95% CI]	[-0.990, -0.831]	[-0.880, -0.719]	[-0.931, -0.700]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.111 [-0.224, 0.002] 0.055
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.095 [-0.235, 0.045] 0.185
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.016 [-0.157, 0.125] 0.824

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12g Statistical Analysis of ACQ-5 total score by Use of Spacer
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.814	-0.728	-0.765		
[95% CI]	[-0.878, -0.750]	[-0.793, -0.663]	[-0.858, -0.673]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.177, 0.006] 0.066
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.049 [-0.162, 0.064] 0.397
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.037 [-0.150, 0.076] 0.522

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13g ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Use of Spacer
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Use of Spacer: Yes	(N=129)	(N=138)	(N=74)
Visit 5 (Week 26)			
Responders	88 (15.4)	91 (15.9)	45 (15.7)
Non-Responders	41 (7.2)	47 (8.2)	29 (10.1)
Change > -0.5	41 (7.2)	47 (8.2)	29 (10.1)
Visit 7 (Week 52)			
Responders	87 (15.2)	91 (15.9)	46 (16.0)
Non-Responders	42 (7.4)	47 (8.2)	28 (9.8)
Change > -0.5	42 (7.4)	47 (8.2)	28 (9.8)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13g ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Use of Spacer
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Use of Spacer: No	(N=442)	(N=433)	(N=213)
Visit 5 (Week 26)			
Responders	279 (48.9)	247 (43.3)	134 (46.7)
Non-Responders	163 (28.5)	186 (32.6)	79 (27.5)
Change > -0.5	161 (28.2)	185 (32.4)	79 (27.5)
Missing data	2 (0.4)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	280 (49.0)	258 (45.2)	128 (44.6)
Non-Responders	162 (28.4)	175 (30.6)	85 (29.6)
Change > -0.5	161 (28.2)	175 (30.6)	85 (29.6)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15g Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Use of Spacer: Yes					
Visit 5 (Week 26)					
Number of Patients Included in Model	129	138	74		
Effect					
Treatment				0.797	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.126 [0.665, 1.905] 0.658/ 1.010 [0.922, 1.107] 0.825/ 0.022 [-0.099, 0.142] 0.725
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.228 [0.662, 2.281] 0.515/ 1.027 [0.923, 1.142] 0.625/ 0.042 [-0.097, 0.180] 0.557
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.917 [0.499, 1.683] 0.779/ 0.984 [0.884, 1.095] 0.766/ -0.020 [-0.158, 0.118] 0.777

Produced: 17 December 2020

Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15g Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	129	138	74		
Effect Treatment Baseline				0.926	<0.001***
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.083 [0.642, 1.826] 0.766/
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.010 [0.915, 1.116] 0.836/
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.016 [-0.101, 0.134] 0.786
					1.121 [0.604, 2.079] 0.717/
					1.024 [0.911, 1.151] 0.692/
					0.029 [-0.107, 0.165] 0.678
					0.966 [0.526, 1.774] 0.911/
					0.987 [0.880, 1.107] 0.821/
					-0.013 [-0.146, 0.121] 0.854

Produced: 17 December 2020

Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15g Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value
Use of Spacer: No					
Visit 5 (Week 26)					
Number of Patients Included in Model	442	433	213		
Effect					
Treatment				0.267	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.217 [0.923, 1.605] 0.164/1.063 [0.960, 1.176] 0.238/0.043 [-0.021, 0.106] 0.185
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.965 [0.684, 1.362] 0.840/0.976 [0.864, 1.103] 0.699/-0.013 [-0.090, 0.064] 0.741
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.261 [0.895, 1.777] 0.185/1.089 [0.959, 1.236] 0.187/0.056 [-0.022, 0.134] 0.162

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15g Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Use of Spacer (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	442	433	213		
Effect Treatment Baseline				0.674 <0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.124 [0.853, 1.480] 0.407/ 1.026 [0.925, 1.138] 0.624/ 0.023 [-0.041, 0.087] 0.489
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.115 [0.795, 1.564] 0.528/ 1.029 [0.904, 1.170] 0.668/ 0.021 [-0.058, 0.100] 0.598
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.008 [0.719, 1.412] 0.965/ 0.998 [0.874, 1.138] 0.972/ 0.001 [-0.079, 0.081] 0.972

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
[2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
[3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	284	134		
Effect					
Treatment				0.213	
Visit Period				0.052	
Treatment*Visit Period				0.476	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.602	-0.516	-0.581		
[95% CI]	[-0.687, -0.517]	[-0.599, -0.433]	[-0.702, -0.460]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.205, 0.033] 0.157
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.021 [-0.169, 0.127] 0.782
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.065 [-0.212, 0.082] 0.386

Produced: 17 December 2020 Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.691	-0.631	-0.725		
[95% CI]	[-0.783, -0.599]	[-0.721, -0.540]	[-0.857, -0.593]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.060 [-0.190, 0.069] 0.359
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.034 [-0.128, 0.195] 0.683
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.094 [-0.254, 0.066] 0.249
Visit 5 (Week 26)					
Adjusted Mean	-0.809	-0.724	-0.752		
[95% CI]	[-0.904, -0.715]	[-0.817, -0.631]	[-0.887, -0.617]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.086 [-0.218, 0.047] 0.205
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.058 [-0.222, 0.107] 0.492
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.028 [-0.191, 0.135] 0.737

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.830	-0.701	-0.831		
[95% CI]	[-0.931, -0.729]	[-0.800, -0.602]	[-0.975, -0.688]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.130 [-0.271, 0.012] 0.073
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.001 [-0.175, 0.177] 0.991
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.131 [-0.305, 0.044] 0.141
Visit 7 (Week 52)					
Adjusted Mean	-0.853	-0.722	-0.731		
[95% CI]	[-0.957, -0.750]	[-0.823, -0.621]	[-0.878, -0.584]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.131 [-0.276, 0.014] 0.075
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.123 [-0.302, 0.057] 0.181
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.009 [-0.187, 0.169] 0.921

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.791	-0.687	-0.751		
[95% CI]	[-0.874, -0.708]	[-0.768, -0.605]	[-0.869, -0.633]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.104 [-0.221, 0.012] 0.079
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.040 [-0.185, 0.105] 0.588
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.064 [-0.208, 0.079] 0.380

Produced: 17 December 2020

Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	296	281	151		
Effect					
Treatment				0.677	
Visit Period				0.175	
Treatment*Visit Period				0.376	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.622	-0.606	-0.630		
[95% CI]	[-0.702, -0.542]	[-0.688, -0.524]	[-0.742, -0.518]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.016 [-0.131, 0.099] 0.785
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.008 [-0.130, 0.146] 0.909
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.024 [-0.163, 0.115] 0.735

Produced: 17 December 2020 Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.798	-0.732	-0.787		
[95% CI]	[-0.883, -0.714]	[-0.819, -0.645]	[-0.906, -0.668]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.066 [-0.188, 0.055] 0.283
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.011 [-0.158, 0.135] 0.877
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.055 [-0.202, 0.092] 0.463
Visit 5 (Week 26)					
Adjusted Mean	-0.880	-0.821	-0.895		
[95% CI]	[-0.974, -0.786]	[-0.917, -0.725]	[-1.027, -0.763]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.058 [-0.193, 0.076] 0.394
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.015 [-0.147, 0.178] 0.853
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.074 [-0.237, 0.090] 0.376

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.895	-0.889	-0.818		
[95% CI]	[-0.988, -0.803]	[-0.983, -0.794]	[-0.949, -0.687]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.007 [-0.139, 0.126] 0.921
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.077 [-0.238, 0.083] 0.345
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.071 [-0.091, 0.232] 0.391
Visit 7 (Week 52)					
Adjusted Mean	-0.993	-0.903	-0.956		
[95% CI]	[-1.087, -0.900]	[-0.999, -0.808]	[-1.089, -0.823]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.090 [-0.224, 0.044] 0.188
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.037 [-0.200, 0.126] 0.654
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.053 [-0.217, 0.111] 0.530

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12h Statistical Analysis of ACQ-5 total score by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.878	-0.828	-0.851		
[95% CI]	[-0.956, -0.800]	[-0.908, -0.749]	[-0.961, -0.742]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.050 [-0.161, 0.062] 0.381
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.026 [-0.161, 0.108] 0.700
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.023 [-0.158, 0.112] 0.736

Produced: 17 December 2020

Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13h ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Relevant Concomitant Cardiovascular Diseases: Yes	(N=273)	(N=287)	(N=134)
Visit 5 (Week 26)			
Responders	171 (29.9)	160 (28.0)	80 (27.9)
Non-Responders	102 (17.9)	127 (22.2)	54 (18.8)
Change > -0.5	101 (17.7)	126 (22.1)	54 (18.8)
Missing data	1 (0.2)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	163 (28.5)	167 (29.2)	79 (27.5)
Non-Responders	110 (19.3)	120 (21.0)	55 (19.2)
Change > -0.5	110 (19.3)	120 (21.0)	55 (19.2)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13h ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Relevant Concomitant Cardiovascular Diseases: No	(N=298)	(N=284)	(N=153)
Visit 5 (Week 26)			
Responders	196 (34.3)	178 (31.2)	99 (34.5)
Non-Responders	102 (17.9)	106 (18.6)	54 (18.8)
Change > -0.5	101 (17.7)	106 (18.6)	54 (18.8)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	204 (35.7)	182 (31.9)	95 (33.1)
Non-Responders	94 (16.5)	102 (17.9)	58 (20.2)
Change > -0.5	93 (16.3)	102 (17.9)	58 (20.2)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15h Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Visit 5 (Week 26)					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.353	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.282 [0.908, 1.811] 0.158/ 1.077 [0.958, 1.211] 0.216/ 0.058 [-0.021, 0.137] 0.153
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.073 [0.697, 1.653] 0.749/ 1.022 [0.884, 1.181] 0.770/ 0.014 [-0.084, 0.112] 0.778
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.195 [0.781, 1.828] 0.411/ 1.054 [0.908, 1.223] 0.491/ 0.044 [-0.055, 0.142] 0.384

Produced: 17 December 2020

Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15h Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.976	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.033 [0.735, 1.452] 0.851/ 1.024 [0.895, 1.172] 0.727/ 0.010 [-0.071, 0.091] 0.805
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.994 [0.650, 1.520] 0.977/ 1.008 [0.853, 1.192] 0.925/ 0.000 [-0.100, 0.101] 0.994
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.040 [0.683, 1.583] 0.856/ 1.016 [0.859, 1.201] 0.852/ 0.010 [-0.090, 0.109] 0.847

Produced: 17 December 2020

Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15h Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Relevant Concomitant Cardiovascular Diseases (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Visit 5 (Week 26)					
Number of Patients Included in Model	298	284	153		
Effect					
Treatment				0.863	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.080 [0.763, 1.530] 0.664/ 1.009 [0.935, 1.089] 0.823/ 0.012 [-0.067, 0.092] 0.764
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.975 [0.641, 1.483] 0.907/ 0.999 [0.916, 1.090] 0.982/ -0.003 [-0.096, 0.089] 0.945
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.108 [0.728, 1.685] 0.633/ 1.010 [0.922, 1.106] 0.834/ 0.015 [-0.079, 0.110] 0.749

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15h Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Relevant Concomitant Cardiovascular Diseases
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	298	284	153		
Effect Treatment Baseline				0.517 <0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.159 [0.816, 1.646] 0.410/ 0.989 [0.881, 1.111] 0.855/ 0.011 [-0.066, 0.087] 0.785
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.256 [0.829, 1.903] 0.282/ 1.050 [0.910, 1.210] 0.505/ 0.039 [-0.052, 0.130] 0.404
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.923 [0.610, 1.397] 0.704/ 0.942 [0.814, 1.091] 0.427/ -0.028 [-0.122, 0.066] 0.559

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	317	315	159		
Effect					
Treatment				0.395	
Visit Period				0.470	
Treatment*Visit Period				0.985	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.608	-0.583	-0.646		
[95% CI]	[-0.685, -0.530]	[-0.661, -0.505]	[-0.755, -0.536]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.025 [-0.135, 0.085] 0.660
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.038 [-0.096, 0.172] 0.579
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.063 [-0.197, 0.072] 0.360

Produced: 17 December 2020

Page 1 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.737	-0.713	-0.813		
[95% CI]	[-0.820, -0.655]	[-0.795, -0.631]	[-0.929, -0.697]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.024 [-0.141, 0.092] 0.680
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.075 [-0.067, 0.217] 0.298
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.100 [-0.242, 0.042] 0.168
Visit 5 (Week 26)					
Adjusted Mean	-0.830	-0.788	-0.893		
[95% CI]	[-0.917, -0.742]	[-0.875, -0.700]	[-1.017, -0.769]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.042 [-0.166, 0.082] 0.504
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.063 [-0.089, 0.215] 0.415
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.105 [-0.257, 0.046] 0.173

Produced: 17 December 2020

Page 2 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.836	-0.798	-0.846		
[95% CI]	[-0.926, -0.746]	[-0.888, -0.707]	[-0.974, -0.718]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.039 [-0.166, 0.089] 0.552
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.010 [-0.147, 0.166] 0.904
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.048 [-0.205, 0.108] 0.545
Visit 7 (Week 52)					
Adjusted Mean	-0.896	-0.840	-0.943		
[95% CI]	[-0.986, -0.806]	[-0.930, -0.751]	[-1.071, -0.816]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.056 [-0.183, 0.071] 0.387
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.047 [-0.109, 0.203] 0.552
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.103 [-0.259, 0.053] 0.194

Produced: 17 December 2020

Page 3 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.815	-0.775	-0.861		
[95% CI]	[-0.889, -0.742]	[-0.849, -0.702]	[-0.965, -0.756]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.040 [-0.144, 0.064] 0.447
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					0.045 [-0.082, 0.172] 0.488
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.085 [-0.213, 0.042] 0.189

Produced: 17 December 2020

Page 4 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	250	126		
Effect					
Treatment				0.095	
Visit Period				0.035*	
Treatment*Visit Period				0.468	
Baseline				<0.001***	
Baseline*Visit Period				<0.001***	
Visit 3 (Week 4)					
Adjusted Mean	-0.618	-0.535	-0.555		
[95% CI]	[-0.706, -0.530]	[-0.624, -0.447]	[-0.680, -0.430]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.083 [-0.208, 0.042] 0.194
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.063 [-0.216, 0.090] 0.419
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.020 [-0.173, 0.133] 0.801

Produced: 17 December 2020

Page 5 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 4 (Week 12)					
Adjusted Mean	-0.759	-0.642	-0.687		
[95% CI]	[-0.855, -0.662]	[-0.739, -0.545]	[-0.823, -0.550]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.117 [-0.254, 0.020] 0.094
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.072 [-0.240, 0.096] 0.399
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.045 [-0.213, 0.123] 0.599
Visit 5 (Week 26)					
Adjusted Mean	-0.867	-0.754	-0.742		
[95% CI]	[-0.970, -0.764]	[-0.857, -0.651]	[-0.888, -0.597]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.113 [-0.259, 0.033] 0.129
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.125 [-0.303, 0.054] 0.170
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.012 [-0.167, 0.190] 0.896

Produced: 17 December 2020

Page 6 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Visit 6 (Week 40)					
Adjusted Mean	-0.899	-0.792	-0.798		
[95% CI]	[-1.005, -0.794]	[-0.898, -0.687]	[-0.947, -0.649]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.107 [-0.256, 0.042] 0.160
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.101 [-0.284, 0.082] 0.277
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					-0.006 [-0.189, 0.177] 0.952
Visit 7 (Week 52)					
Adjusted Mean	-0.967	-0.779	-0.726		
[95% CI]	[-1.078, -0.857]	[-0.890, -0.668]	[-0.882, -0.569]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.189 [-0.345, -0.032] 0.018*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.242 [-0.434, -0.050] 0.014*
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.053 [-0.139, 0.245] 0.586

Produced: 17 December 2020

Page 7 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.12i Statistical Analysis of ACQ-5 total score by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Mean Difference [95% CI] p-value
Overall					
Adjusted Mean	-0.863	-0.736	-0.730		
[95% CI]	[-0.953, -0.774]	[-0.826, -0.646]	[-0.857, -0.604]		
p-value	<0.001***	<0.001***	<0.001***		
CHF 5993 pMDI - CHF 1535 pMDI					-0.127 [-0.254, -0.000] 0.050*
CHF 5993 pMDI HS - CHF 1535 pMDI HS + Tiotropium					-0.133 [-0.288, 0.023] 0.094
CHF 1535 pMDI HS + Tiotropium - CHF 1535 pMDI HS					0.006 [-0.150, 0.161] 0.944

Produced: 17 December 2020 Page 8 of 8

Source: Listing Not Available

Notes: [1] Analysis is based on a linear mixed model for repeated measures including treatment, visit period, treatment by visit period interaction as fixed effects, and baseline value and baseline by visit period interaction as covariates

[2] Data from patients who discontinued prematurely are re-allocated to the next expected visit period

Table 18.2.13i ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Region
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Region: Europe	(N=319)	(N=319)	(N=160)
Visit 5 (Week 26)			
Responders	196 (34.3)	191 (33.5)	106 (36.9)
Non-Responders	123 (21.5)	128 (22.4)	54 (18.8)
Change > -0.5	121 (21.2)	128 (22.4)	54 (18.8)
Missing data	2 (0.4)	0 (0.0)	0 (0.0)
Visit 7 (Week 52)			
Responders	207 (36.3)	197 (34.5)	103 (35.9)
Non-Responders	112 (19.6)	122 (21.4)	57 (19.9)
Change > -0.5	112 (19.6)	122 (21.4)	57 (19.9)

Produced: 17 December 2020

Page 1 of 2

Source: Not Applicable

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
 [2] Table presents number and percentage of patients (n (%))
 [3] Percentages are based on the number of patients in the relevant treatment/population (N)
 [4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.13i ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Region
(Intention-to-Treat Population)

Visit	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)
Region: Rest of World	(N=252)	(N=252)	(N=127)
Visit 5 (Week 26)			
Responders	171 (29.9)	147 (25.7)	73 (25.4)
Non-Responders	81 (14.2)	105 (18.4)	54 (18.8)
Change > -0.5	81 (14.2)	104 (18.2)	54 (18.8)
Missing data	0 (0.0)	1 (0.2)	0 (0.0)
Visit 7 (Week 52)			
Responders	160 (28.0)	152 (26.6)	71 (24.7)
Non-Responders	92 (16.1)	100 (17.5)	56 (19.5)
Change > -0.5	91 (15.9)	100 (17.5)	56 (19.5)
Missing data	1 (0.2)	0 (0.0)	0 (0.0)

Produced: 17 December 2020

Page 2 of 2

Source: Not Applicable

Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data

[2] Table presents number and percentage of patients (n (%))

[3] Percentages are based on the number of patients in the relevant treatment/population (N)

[4] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15i Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Region: Yes					
Visit 5 (Week 26)					
Number of Patients Included in Model	319	319	160		
Effect					
Treatment				0.366	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.975 [0.702, 1.355] 0.880/ 0.998 [0.943, 1.057] 0.954/ 0.016 [-0.060, 0.091] 0.685
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.754 [0.501, 1.136] 0.177/ 0.977 [0.915, 1.043] 0.479/ -0.048 [-0.139, 0.043] 0.299
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.293 [0.859, 1.945] 0.218/ 1.022 [0.956, 1.093] 0.524/ 0.064 [-0.027, 0.155] 0.169

Produced: 17 December 2020

Page 1 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score \leq -0.5; non-response = change from baseline in ACQ-5 score $>$ -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15i Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	319	319	160		
Effect Treatment Baseline				0.875	<0.001***
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.072 [0.772, 1.490] 0.678/ 1.011 [0.936, 1.092] 0.780/ 0.031 [-0.043, 0.106] 0.411
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.978 [0.653, 1.464] 0.915/ 0.997 [0.910, 1.092] 0.941/ 0.005 [-0.086, 0.096] 0.911
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.096 [0.734, 1.637] 0.654/ 1.015 [0.924, 1.114] 0.762/ 0.026 [-0.065, 0.118] 0.574

Produced: 17 December 2020

Page 2 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15i Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Region
(Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Region: No					
Visit 5 (Week 26)					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.071	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.492 [1.031, 2.158] 0.034*/ 1.135 [0.999, 1.289] 0.053/ 0.095 [0.011, 0.179] 0.026*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.482 [0.948, 2.316] 0.085/ 1.131 [0.955, 1.341] 0.154/ 0.104 [0.000, 0.207] 0.049*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.007 [0.649, 1.561] 0.976/ 1.003 [0.839, 1.199] 0.975/ -0.009 [-0.114, 0.097] 0.874

Produced: 17 December 2020

Page 3 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score ≤ -0.5 ; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

Table 18.2.15i Statistical Analysis of ACQ-5 response at Visit 5 (Week 26) and Visit 7 (Week 52) by Region (Intention-to-Treat Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Odds Ratio [95% CI] p-value /Relative Risk [95% CI] p-value /Risk Difference [95% CI] p-value
Visit 7 (Week 52)					
Number of Patients Included in Model	252	252	127		
Effect					
Treatment				0.476	
Baseline				<0.001***	
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.127 [0.784, 1.620] 0.519/ 1.030 [0.901, 1.178] 0.666/ 0.032 [-0.053, 0.116] 0.463
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.311 [0.845, 2.033] 0.227/ 1.105 [0.925, 1.320] 0.271/ 0.076 [-0.029, 0.181] 0.156
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.860 [0.556, 1.330] 0.497/ 0.932 [0.778, 1.117] 0.445/ -0.044 [-0.150, 0.061] 0.412

Produced: 17 December 2020

Page 4 of 4

Source: Not available

- Notes: [1] ACQ-5 response = change from baseline in ACQ-5 score <= -0.5; non-response = change from baseline in ACQ-5 score > -0.5 or missing data
 [2] Analysis is based on a logistic model including treatment and the baseline ACQ-5 score value as a covariate
 [3] Data from patients who discontinued prematurely and performed the Visit 7 assessments are re-allocated to the most appropriate visit

ADDITIONAL_TLF_BATCH2_ADVERSE_EVENTS

Additional TLF

PROTOCOL NUMBER: CCD-05993AB2-02

Version: Batch2

Date of Production: 17/12/2020

Identification Code: Additional_TLF_batch2_Adverse_Events_CCD-05993AB2-02_20201217(Batch2)

Table 21.2.11a Statistical Analysis of Treatment Emergent Adverse Events including Age Group - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.943
Sex			0.294
Age Group			0.869
Age Group Treatment Interaction			0.746

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.11b Statistical Analysis of Treatment Emergent Adverse Events including Gender - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.947
Age group (< 65 years, >= 65 years)			0.945
Gender			0.189
Gender Treatment Interaction			0.334

Produced: 17 December 2020 Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.11c Statistical Analysis of Treatment Emergent Adverse Events including BMI Class - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.684
Sex			0.389
Age group (< 65 years, >= 65 years)			0.970
BMI Class			0.099
BMI Class Treatment Interaction			0.476

Produced: 17 December 2020 Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and BMI Class

Table 21.2.11d Statistical Analysis of Treatment Emergent Adverse Events including Smoking Status - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.555
Sex			0.156
Age group (< 65 years, >= 65 years)			0.902
Smoking Status			0.018*
Smoking Status Treatment Interaction			0.479

Produced: 17 December 2020 Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.11e Statistical Analysis of Treatment Emergent Adverse Events including Number of Exacerbation in the Previous year - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.769
Sex			0.417
Age group (< 65 years, >= 65 years)			0.979
Number of Exacerbation in the Previous year			0.037*
Number of Exacerbation in the Previous year Treatment Interaction			0.259

Produced: 17 December 2020 Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.11f Statistical Analysis of Treatment Emergent Adverse Events including Degree of reversibility at screening - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	570	287	
Effect			
Treatment			0.756
Sex			0.500
Age group (< 65 years, >= 65 years)			0.764
Degree of reversibility at screening			0.392
Degree of reversibility at screening Treatment Interaction			0.173

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.11g Statistical Analysis of Treatment Emergent Adverse Events
including Use of Spacer - Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.776
Sex			0.317
Age group (< 65 years, >= 65 years)			0.957
Use of Spacer			0.926
Use of Spacer Treatment Interaction			0.347

Produced: 17 December 2020 Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.11h Statistical Analysis of Treatment Emergent Adverse Events
including Relevant Concomitant Cardiovascular Diseases - Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.749
Sex			0.412
Age group (< 65 years, >= 65 years)			0.285
Relevant Concomitant Cardiovascular Diseases			0.005**
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.059

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.11i Statistical Analysis of Treatment Emergent Adverse Events including Region - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.770
Sex			0.316
Age group (< 65 years, >= 65 years)			0.993
Region			0.183
Region Treatment Interaction			0.073

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.12a Statistical Analysis of Treatment Emergent Adverse Events including Age Group, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.925
Sex			0.376
Age Group			0.755
Age Group Treatment Interaction			0.714

Produced: 17 December 2020 Page 1 of 1
 Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8
 Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.12b Statistical Analysis of Treatment Emergent Adverse Events including Gender, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.839
Age group (< 65 years, >= 65 years)			0.828
Gender			0.250
Gender Treatment Interaction			0.341

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.12c Statistical Analysis of Treatment Emergent Adverse Events including BMI Class, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.512
Sex			0.479
Age group (< 65 years, >= 65 years)			0.876
BMI Class			0.137
BMI Class Treatment Interaction			0.543

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and BMI Class

Table 21.2.12d Statistical Analysis of Treatment Emergent Adverse Events including Smoking Status, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.565
Sex			0.235
Age group (< 65 years, >= 65 years)			0.963
Smoking Status			0.048*
Smoking Status Treatment Interaction			0.721

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.12e Statistical Analysis of Treatment Emergent Adverse Events including Number of Exacerbation in the Previous year,
excluding Severe Asthma Exacerbations - Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.830
Sex			0.493
Age group (< 65 years, >= 65 years)			0.859
Number of Exacerbation in the Previous year			0.215
Number of Exacerbation in the Previous year Treatment Interaction			0.207

Produced: 17 December 2020 Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.12f Statistical Analysis of Treatment Emergent Adverse Events including Degree of reversibility at screening, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	570	287	
Effect			
Treatment			0.566
Sex			0.588
Age group (< 65 years, >= 65 years)			0.681
Degree of reversibility at screening			0.480
Degree of reversibility at screening Treatment Interaction			0.173

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.12g Statistical Analysis of Treatment Emergent Adverse Events including Use of Spacer, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.931
Sex			0.411
Age group (< 65 years, >= 65 years)			0.841
Use of Spacer			0.927
Use of Spacer Treatment Interaction			0.305

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.12h Statistical Analysis of Treatment Emergent Adverse Events including Relevant Concomitant Cardiovascular Diseases, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.550
Sex			0.521
Age group (< 65 years, >= 65 years)			0.234
Relevant Concomitant Cardiovascular Diseases			0.005**
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.056

Produced: 17 December 2020 Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.12i Statistical Analysis of Treatment Emergent Adverse Events including Region, excluding Severe Asthma Exacerbations - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.589
Sex			0.426
Age group (< 65 years, >= 65 years)			0.874
Region			0.091
Region Treatment Interaction			0.043*

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.13a Statistical Analysis of Serious Treatment Emergent Adverse Event including Age Group - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.903
Sex			0.247
Age Group			0.957
Age Group Treatment Interaction			0.784

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.13b Statistical Analysis of Serious Treatment Emergent Adverse Event including Gender - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.692
Age group (< 65 years, >= 65 years)			0.796
Gender			0.144
Gender Treatment Interaction			0.294

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.13c Statistical Analysis of Serious Treatment Emergent Adverse Event including BMI Class - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.949
Sex			0.280
Age group (< 65 years, >= 65 years)			0.980
BMI Class			0.128
BMI Class Treatment Interaction			0.945

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and BMI Class

Table 21.2.13d Statistical Analysis of Serious Treatment Emergent Adverse Event including Smoking Status - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.721
Sex			0.247
Age group (< 65 years, >= 65 years)			0.843
Smoking Status			0.825
Smoking Status Treatment Interaction			0.688

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.13e Statistical Analysis of Serious Treatment Emergent Adverse Event including Number of Exacerbation in the Previous year - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.909
Sex			0.339
Age group (< 65 years, >= 65 years)			0.851
Number of Exacerbation in the Previous year			0.221
Number of Exacerbation in the Previous year Treatment Interaction			0.951

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.13f Statistical Analysis of Serious Treatment Emergent Adverse Event including Degree of reversibility at screening - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	570	287	
Effect			
Treatment			0.870
Sex			0.156
Age group (< 65 years, >= 65 years)			0.686
Degree of reversibility at screening			0.230
Degree of reversibility at screening Treatment Interaction			0.568

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.13g Statistical Analysis of Serious Treatment Emergent Adverse Event including Use of Spacer - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.494
Sex			0.207
Age group (< 65 years, >= 65 years)			0.874
Use of Spacer			0.284
Use of Spacer Treatment Interaction			0.051

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.13h Statistical Analysis of Serious Treatment Emergent Adverse Event including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.842
Sex			0.378
Age group (< 65 years, >= 65 years)			0.600
Relevant Concomitant Cardiovascular Diseases			0.006**
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.591

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.13i Statistical Analysis of Serious Treatment Emergent Adverse Event including Region - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.724
Sex			0.241
Age group (< 65 years, >= 65 years)			0.805
Region			0.686
Region Treatment Interaction			0.153

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.14a Statistical Analysis of Serious Treatment Emergent Adverse Events including Age Group, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.849
Age Group			0.707
Age Group Treatment Interaction			0.564

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.14c Statistical Analysis of Serious Treatment Emergent Adverse Events including BMI Class, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.813
Sex			0.837
Age group (< 65 years, >= 65 years)			0.823
BMI Class			0.108
BMI Class Treatment Interaction			0.975

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and BMI Class

Table 21.2.14d Statistical Analysis of Serious Treatment Emergent Adverse Events including Smoking Status, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.677
Age group (< 65 years, >= 65 years)			0.896
Smoking Status			0.869
Smoking Status Treatment Interaction			0.851

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and Smoking Status

Table 21.2.14e Statistical Analysis of Serious Treatment Emergent Adverse Events

including Number of Exacerbation in the Previous year, excluding Severe Asthma Exacerbations
Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.561
Age group (< 65 years, >= 65 years)			0.909
Number of Exacerbation in the Previous year			0.217
Number of Exacerbation in the Previous year Treatment Interaction			0.636

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and Number of Exacerbation in the Previous year

Table 21.2.14f Statistical Analysis of Serious Treatment Emergent Adverse Events including Degree of reversibility at screening, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.677
Sex			0.516
Age group (< 65 years, >= 65 years)			0.951
Degree of reversibility at screening			0.173
Degree of reversibility at screening Treatment Interaction			0.772

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.14g Statistical Analysis of Serious Treatment Emergent Adverse Events including Use of Spacer, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.408
Age group (< 65 years, >= 65 years)			0.904
Use of Spacer			0.323
Use of Spacer Treatment Interaction			0.124

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and Use of Spacer

Table 21.2.14h Statistical Analysis of Serious Treatment Emergent Adverse Events

including Relevant Concomitant Cardiovascular Diseases, excluding Severe Asthma Exacerbations
Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.828
Sex			0.962
Age group (< 65 years, >= 65 years)			0.422
Relevant Concomitant Cardiovascular Diseases			0.006**
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.856

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.14i Statistical Analysis of Serious Treatment Emergent Adverse Events including Region, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.590
Sex			0.711
Age group (< 65 years, >= 65 years)			0.956
Region			0.749
Region Treatment Interaction			0.356

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.15a Statistical Analysis of Severe Treatment Emergent Adverse Events including Age Group - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.232
Sex			0.617
Age Group			0.513
Age Group Treatment Interaction			0.615

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.15b Statistical Analysis of Severe Treatment Emergent Adverse Events
including Gender - Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.215
Age group (< 65 years, >= 65 years)			0.225
Gender			0.499
Gender Treatment Interaction			0.676

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.15c Statistical Analysis of Severe Treatment Emergent Adverse Events including BMI Class - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.249
Sex			0.729
Age group (< 65 years, >= 65 years)			0.292
BMI Class			0.057
BMI Class Treatment Interaction			0.964

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and BMI Class

Table 21.2.15d Statistical Analysis of Severe Treatment Emergent Adverse Events
including Smoking Status - Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.604
Sex			0.394
Age group (< 65 years, >= 65 years)			0.167
Smoking Status			0.033*
Smoking Status Treatment Interaction			0.284

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.15e Statistical Analysis of Severe Treatment Emergent Adverse Events including Number of Exacerbation in the Previous year - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.345
Sex			0.654
Age group (< 65 years, >= 65 years)			0.232
Number of Exacerbation in the Previous year			0.320
Number of Exacerbation in the Previous year Treatment Interaction			0.867

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.15f Statistical Analysis of Severe Treatment Emergent Adverse Events including Degree of reversibility at screening - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	570	287	
Effect			
Treatment			0.281
Sex			0.891
Degree of reversibility at screening			0.205
Degree of reversibility at screening Treatment Interaction			0.565

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, sex and Degree of reversibility at screening

Table 21.2.15g Statistical Analysis of Severe Treatment Emergent Adverse Events
including Use of Spacer - Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.442
Sex			0.569
Age group (< 65 years, >= 65 years)			0.239
Use of Spacer			0.821
Use of Spacer Treatment Interaction			0.638

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.15h Statistical Analysis of Severe Treatment Emergent Adverse Events including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.290
Relevant Concomitant Cardiovascular Diseases			0.003**
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.816

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and Relevant Concomitant Cardiovascular Diseases

Table 21.2.15i Statistical Analysis of Severe Treatment Emergent Adverse Events
including Region - Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.229
Region			0.107
Region Treatment Interaction			0.876

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and Region

Table 21.2.16a Statistical Analysis of Severe Treatment Emergent Adverse Events including Age Group, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.951
Sex			0.796
Age Group			0.959
Age Group Treatment Interaction			0.957

Produced: 17 December 2020 Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.16c Statistical Analysis of Severe Treatment Emergent Adverse Events including BMI Class, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.985
Sex			0.891
BMI Class			0.879
BMI Class Treatment Interaction			0.899

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, sex, BMI Class

Notes: [1] Analysis is based on a negative binomial model including treatment, BMI Class

Table 21.2.16d Statistical Analysis of Severe Treatment Emergent Adverse Events including Smoking Status, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.412
Sex			0.649
Age group (< 65 years, >= 65 years)			0.943
Smoking Status			0.156
Smoking Status Treatment Interaction			0.377

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.16e Statistical Analysis of Severe Treatment Emergent Adverse Events

including Number of Exacerbation in the Previous year, excluding Severe Asthma Exacerbations
Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.431
Number of Exacerbation in the Previous year			0.457
Number of Exacerbation in the Previous year Treatment Interaction			0.341

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Table 21.2.16f Statistical Analysis of Severe Treatment Emergent Adverse Events including Degree of reversibility at screening, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.241
Sex			0.775
Age group (< 65 years, >= 65 years)			0.970
Degree of reversibility at screening			0.902
Degree of reversibility at screening Treatment Interaction			0.967

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.16g Statistical Analysis of Severe Treatment Emergent Adverse Events including Use of Spacer, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.230
Sex			0.852
Age group (< 65 years, >= 65 years)			0.979
Use of Spacer			0.237
Use of Spacer Treatment Interaction			0.890

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.16h Statistical Analysis of Severe Treatment Emergent Adverse Events

including Relevant Concomitant Cardiovascular Diseases, excluding Severe Asthma Exacerbations
Interaction Test
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.965
Relevant Concomitant Cardiovascular Diseases			0.963
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.968

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, Relevant Concomitant Cardiovascular Diseases

Table 21.2.16i Statistical Analysis of Severe Treatment Emergent Adverse Events including Region, excluding Severe Asthma Exacerbations Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.255
Region			0.583
Region Treatment Interaction			0.794

Produced: 17 December 2020

Page 1 of 1

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, Region

Table 21.2.17a Statistical Analysis of Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	450	246		
Effect					
Treatment				0.238	
Sex				0.101	
Adjusted Rate per Patient per Year [95% CI]	3.000 [2.697, 3.337]	3.410 [3.059, 3.801]	3.090 [2.662, 3.586]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.880 [0.755, 1.024] 0.099
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.971 [0.808, 1.166] 0.752
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.906 [0.753, 1.090] 0.295

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment and sex

Table 21.2.17a Statistical Analysis of Treatment Emergent Adverse Events by Age Group
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.758	
Sex				0.654	
Adjusted Rate per Patient per Year [95% CI]	3.024 [2.388, 3.830]	3.336 [2.704, 4.116]	2.924 [2.012, 4.251]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.907 [0.661, 1.243] 0.543
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.034 [0.664, 1.610] 0.882
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.877 [0.571, 1.346] 0.547

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment and sex

Table 21.2.17b Statistical Analysis of Treatment Emergent Adverse Events by Gender
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	245	103		
Effect					
Treatment				0.405	
Age group (< 65 years, >= 65 years)				0.480	
Adjusted Rate per Patient per Year [95% CI]	2.949 [2.503, 3.474]	3.246 [2.789, 3.777]	2.698 [2.127, 3.422]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.909 [0.727, 1.136] 0.400
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.093 [0.819, 1.459] 0.547
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.831 [0.627, 1.102] 0.199

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.17b Statistical Analysis of Treatment Emergent Adverse Events by Gender
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	328	184		
Effect					
Treatment				0.299	
Age group (< 65 years, >= 65 years)				0.401	
Adjusted Rate per Patient per Year [95% CI]	3.045 [2.700, 3.435]	3.494 [3.083, 3.960]	3.294 [2.779, 3.904]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.872 [0.733, 1.037] 0.122
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.925 [0.751, 1.139] 0.461
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.943 [0.763, 1.165] 0.584

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.17c Statistical Analysis of Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.400	
Sex				0.409	
Age group (< 65 years, >= 65 years)				0.980	
Adjusted Rate per Patient per Year [95% CI]	2.643 [2.160, 3.234]	3.102 [2.571, 3.743]	3.241 [2.439, 4.306]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.852 [0.647, 1.123] 0.255
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.815 [0.575, 1.156] 0.252
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.045 [0.743, 1.469] 0.801

Produced: 17 December 2020

Page 1 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17c Statistical Analysis of Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.263	
Sex				0.030*	
Age group (< 65 years, >= 65 years)				0.814	
Adjusted Rate per Patient per Year [95% CI]	2.824 [2.408, 3.312]	3.267 [2.767, 3.857]	2.632 [2.090, 3.315]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.865 [0.687, 1.088] 0.216
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.073 [0.811, 1.420] 0.622
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.806 [0.606, 1.070] 0.136

Produced: 17 December 2020

Page 2 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17c Statistical Analysis of Treatment Emergent Adverse Events by BMI Class
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	205	102		
Effect					
Treatment				0.646	
Sex				0.640	
Age group (< 65 years, >= 65 years)				0.790	
Adjusted Rate per Patient per Year [95% CI]	3.444 [2.957, 4.010]	3.760 [3.231, 4.377]	3.387 [2.726, 4.207]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.916 [0.738, 1.136] 0.423
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.017 [0.780, 1.325] 0.902
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.901 [0.690, 1.176] 0.441

Produced: 17 December 2020

Page 3 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17d Statistical Analysis of Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	493	245		
Effect					
Treatment				0.190	
Sex				0.304	
Age group (< 65 years, >= 65 years)				0.974	
Adjusted Rate per Patient per Year [95% CI]	2.925 [2.629, 3.254]	3.308 [2.975, 3.678]	2.885 [2.475, 3.363]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.884 [0.761, 1.028] 0.109
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.014 [0.841, 1.221] 0.887
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.872 [0.724, 1.051] 0.151

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17d Statistical Analysis of Treatment Emergent Adverse Events by Smoking Status
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.638	
Sex				0.058	
Age group (< 65 years, >= 65 years)				0.916	
Adjusted Rate per Patient per Year [95% CI]	3.456 [2.743, 4.354]	3.910 [3.102, 4.929]	4.092 [2.976, 5.626]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.884 [0.636, 1.229] 0.463
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.845 [0.571, 1.249] 0.398
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.046 [0.704, 1.556] 0.823

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17e Statistical Analysis of Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	452	229		
Effect					
Treatment				0.068	
Sex				0.444	
Age group (< 65 years, >= 65 years)				0.935	
Adjusted Rate per Patient per Year [95% CI]	2.742 [2.449, 3.071]	3.306 [2.961, 3.692]	3.005 [2.570, 3.513]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.829 [0.708, 0.972] 0.020*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.913 [0.753, 1.107] 0.353
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.909 [0.750, 1.101] 0.328

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17e Statistical Analysis of Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	121	58		
Effect					
Treatment				0.643	
Sex				0.416	
Age group (< 65 years, >= 65 years)				0.985	
Adjusted Rate per Patient per Year [95% CI]	3.909 [3.243, 4.711]	3.723 [3.059, 4.531]	3.305 [2.457, 4.445]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.050 [0.800, 1.377] 0.725
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.183 [0.833, 1.679] 0.348
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.888 [0.622, 1.267] 0.512

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17f Statistical Analysis of Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	299	283	147		
Effect					
Treatment				0.372	
Sex				0.802	
Age group (< 65 years, >= 65 years)				0.404	
Adjusted Rate per Patient per Year [95% CI]	3.309 [2.906, 3.769]	3.534 [3.087, 4.046]	2.985 [2.462, 3.618]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.936 [0.776, 1.130] 0.493
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.109 [0.879, 1.398] 0.383
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.845 [0.667, 1.070] 0.161

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17f Statistical Analysis of Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.168	
Sex				0.337	
Age group (< 65 years, >= 65 years)				0.726	
Adjusted Rate per Patient per Year [95% CI]	2.698 [2.332, 3.121]	3.259 [2.840, 3.740]	3.116 [2.552, 3.806]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.828 [0.678, 1.012] 0.065
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.866 [0.676, 1.109] 0.253
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.956 [0.750, 1.219] 0.718

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17g Statistical Analysis of Treatment Emergent Adverse Events by Use of Spacer
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	139	74		
Effect					
Treatment				0.073	
Sex				0.072	
Age group (< 65 years, >= 65 years)				0.088	
Adjusted Rate per Patient per Year [95% CI]	3.260 [2.660, 3.996]	4.082 [3.349, 4.975]	2.804 [2.133, 3.687]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.799 [0.601, 1.061] 0.121
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.163 [0.827, 1.634] 0.386
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.687 [0.489, 0.964] 0.030*

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17g Statistical Analysis of Treatment Emergent Adverse Events by Use of Spacer
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	434	213		
Effect					
Treatment				0.567	
Sex				0.698	
Age group (< 65 years, >= 65 years)				0.494	
Adjusted Rate per Patient per Year [95% CI]	2.932 [2.626, 3.274]	3.181 [2.848, 3.552]	3.140 [2.675, 3.687]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.922 [0.789, 1.078] 0.308
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.934 [0.769, 1.134] 0.490
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.987 [0.812, 1.200] 0.898

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17h Statistical Analysis of Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.242	
Sex				0.747	
Age group (< 65 years, >= 65 years)				0.107	
Adjusted Rate per Patient per Year [95% CI]	3.620 [3.195, 4.102]	3.830 [3.390, 4.327]	3.168 [2.639, 3.803]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.945 [0.793, 1.126] 0.528
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.143 [0.916, 1.425] 0.237
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.827 [0.663, 1.032] 0.092

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17h Statistical Analysis of Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	286	153		
Effect					
Treatment				0.133	
Sex				0.082	
Age group (< 65 years, >= 65 years)				0.549	
Adjusted Rate per Patient per Year [95% CI]	2.432 [2.095, 2.822]	2.955 [2.542, 3.436]	2.975 [2.415, 3.664]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.823 [0.666, 1.017] 0.071
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.817 [0.633, 1.056] 0.123
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.007 [0.778, 1.302] 0.960

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17i Statistical Analysis of Treatment Emergent Adverse Events by Region
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	320	160		
Effect					
Treatment				0.136	
Sex				0.202	
Age group (< 65 years, >= 65 years)				0.526	
Adjusted Rate per Patient per Year [95% CI]	3.059 [2.693, 3.474]	3.353 [2.954, 3.806]	2.670 [2.216, 3.216]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.912 [0.762, 1.092] 0.316
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.146 [0.914, 1.436] 0.237
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.796 [0.635, 0.997] 0.047*

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.17i Statistical Analysis of Treatment Emergent Adverse Events by Region
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	253	127		
Effect					
Treatment				0.211	
Sex				0.647	
Age group (< 65 years, >= 65 years)				0.433	
Adjusted Rate per Patient per Year [95% CI]	2.931 [2.525, 3.402]	3.455 [2.980, 4.007]	3.529 [2.866, 4.345]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.848 [0.687, 1.047] 0.126
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.830 [0.643, 1.072] 0.154
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.021 [0.790, 1.320] 0.872

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18a Statistical Analysis of Treatment Emergent Adverse Events by Age Group, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	450	246		
Effect					
Treatment				0.331	
Sex				0.110	
Adjusted Rate per Patient per Year [95% CI]	2.690 [2.413, 2.999]	3.027 [2.709, 3.382]	2.846 [2.446, 3.313]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.889 [0.761, 1.038] 0.137
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.945 [0.784, 1.139] 0.554
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.940 [0.779, 1.135] 0.521

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment and sex

Table 21.2.18a Statistical Analysis of Treatment Emergent Adverse Events by Age Group, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.843	
Sex				0.540	
Adjusted Rate per Patient per Year [95% CI]	2.676 [2.099, 3.410]	2.910 [2.346, 3.611]	2.638 [1.799, 3.869]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.919 [0.665, 1.272] 0.612
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.014 [0.644, 1.597] 0.951
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.907 [0.584, 1.407] 0.662

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment and sex

Table 21.2.18b Statistical Analysis of Treatment Emergent Adverse Events by Gender, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	245	103		
Effect					
Treatment				0.621	
Age group (< 65 years, >= 65 years)				0.495	
Adjusted Rate per Patient per Year [95% CI]	2.659 [2.251, 3.140]	2.861 [2.452, 3.340]	2.500 [1.964, 3.182]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.929 [0.741, 1.166] 0.527
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.064 [0.793, 1.426] 0.680
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.874 [0.656, 1.164] 0.356

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.18b Statistical Analysis of Treatment Emergent Adverse Events by Gender, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	328	184		
Effect					
Treatment				0.307	
Age group (< 65 years, >= 65 years)				0.277	
Adjusted Rate per Patient per Year [95% CI]	2.710 [2.395, 3.066]	3.101 [2.728, 3.525]	3.008 [2.528, 3.579]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.874 [0.731, 1.044] 0.138
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.901 [0.728, 1.115] 0.336
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.970 [0.782, 1.204] 0.783

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.18c Statistical Analysis of Treatment Emergent Adverse Events by BMI Class, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.452	
Sex				0.612	
Age group (< 65 years, >= 65 years)				0.872	
Adjusted Rate per Patient per Year [95% CI]	2.409 [1.961, 2.960]	2.748 [2.267, 3.331]	2.981 [2.230, 3.984]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.877 [0.661, 1.162] 0.360
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.808 [0.566, 1.154] 0.241
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.085 [0.766, 1.536] 0.647

Produced: 17 December 2020

Page 1 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18c Statistical Analysis of Treatment Emergent Adverse Events by BMI Class, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.311	
Sex				0.052	
Age group (< 65 years, >= 65 years)				0.915	
Adjusted Rate per Patient per Year [95% CI]	2.533 [2.154, 2.980]	2.948 [2.490, 3.490]	2.431 [1.923, 3.072]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.859 [0.680, 1.087] 0.205
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.042 [0.784, 1.386] 0.776
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.825 [0.618, 1.101] 0.190

Produced: 17 December 2020

Page 2 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18c Statistical Analysis of Treatment Emergent Adverse Events by BMI Class, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	205	102		
Effect					
Treatment				0.813	
Sex				0.840	
Age group (< 65 years, >= 65 years)				0.588	
Adjusted Rate per Patient per Year [95% CI]	3.048 [2.607, 3.565]	3.270 [2.797, 3.823]	3.087 [2.472, 3.855]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.932 [0.747, 1.163] 0.534
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.987 [0.753, 1.295] 0.927
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.944 [0.718, 1.241] 0.680

Produced: 17 December 2020

Page 3 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18d Statistical Analysis of Treatment Emergent Adverse Events by Smoking Status, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	493	245		
Effect					
Treatment				0.341	
Sex				0.368	
Age group (< 65 years, >= 65 years)				0.743	
Adjusted Rate per Patient per Year [95% CI]	2.617 [2.347, 2.918]	2.928 [2.627, 3.263]	2.690 [2.301, 3.144]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.894 [0.766, 1.042] 0.152
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.973 [0.804, 1.177] 0.778
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.919 [0.759, 1.111] 0.382

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18d Statistical Analysis of Treatment Emergent Adverse Events by Smoking Status, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.767	
Sex				0.078	
Age group (< 65 years, >= 65 years)				0.941	
Adjusted Rate per Patient per Year [95% CI]	3.107 [2.451, 3.938]	3.439 [2.710, 4.365]	3.536 [2.547, 4.908]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.903 [0.644, 1.268] 0.557
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.879 [0.587, 1.314] 0.529
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.028 [0.683, 1.547] 0.895

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18e Statistical Analysis of Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	452	229		
Effect					
Treatment				0.091	
Sex				0.516	
Age group (< 65 years, >= 65 years)				0.809	
Adjusted Rate per Patient per Year [95% CI]	2.506 [2.231, 2.813]	2.999 [2.678, 3.358]	2.818 [2.402, 3.307]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.836 [0.710, 0.983] 0.030*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.889 [0.730, 1.083] 0.243
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.940 [0.772, 1.144] 0.535

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18e Statistical Analysis of Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	121	58		
Effect					
Treatment				0.573	
Sex				0.327	
Age group (< 65 years, >= 65 years)				0.862	
Adjusted Rate per Patient per Year [95% CI]	3.319 [2.749, 4.008]	3.028 [2.479, 3.697]	2.765 [2.046, 3.738]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.096 [0.833, 1.443] 0.512
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.200 [0.841, 1.712] 0.314
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.913 [0.636, 1.312] 0.624

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18f Statistical Analysis of Treatment Emergent Adverse Events by Degree of reversibility at screening, excluding Severe Asthma Exacerbations
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	299	283	147		
Effect					
Treatment				0.506	
Sex				0.838	
Age group (< 65 years, >= 65 years)				0.263	
Adjusted Rate per Patient per Year [95% CI]	2.943 [2.577, 3.359]	3.124 [2.721, 3.586]	2.710 [2.228, 3.296]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.942 [0.778, 1.141] 0.540
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.086 [0.858, 1.375] 0.494
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.867 [0.682, 1.103] 0.246

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18f Statistical Analysis of Treatment Emergent Adverse Events by Degree of reversibility at screening, excluding Severe Asthma Exacerbations
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.209	
Sex				0.382	
Age group (< 65 years, >= 65 years)				0.670	
Adjusted Rate per Patient per Year [95% CI]	2.434 [2.098, 2.825]	2.888 [2.508, 3.325]	2.884 [2.352, 3.537]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.843 [0.687, 1.035] 0.102
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.844 [0.656, 1.087] 0.188
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.999 [0.779, 1.280] 0.992

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18g Statistical Analysis of Treatment Emergent Adverse Events by Use of Spacer, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	139	74		
Effect					
Treatment				0.191	
Sex				0.062	
Age group (< 65 years, >= 65 years)				0.096	
Adjusted Rate per Patient per Year [95% CI]	2.932 [2.389, 3.600]	3.474 [2.843, 4.244]	2.555 [1.939, 3.366]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.844 [0.634, 1.125] 0.247
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.148 [0.814, 1.618] 0.432
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.736 [0.522, 1.036] 0.079

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18g Statistical Analysis of Treatment Emergent Adverse Events by Use of Spacer, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	434	213		
Effect					
Treatment				0.475	
Sex				0.790	
Age group (< 65 years, >= 65 years)				0.683	
Adjusted Rate per Patient per Year [95% CI]	2.619 [2.338, 2.933]	2.857 [2.550, 3.200]	2.891 [2.453, 3.408]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.917 [0.781, 1.076] 0.288
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.906 [0.742, 1.106] 0.330
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.012 [0.829, 1.236] 0.906

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18h Statistical Analysis of Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.423	
Sex				0.750	
Age group (< 65 years, >= 65 years)				0.070	
Adjusted Rate per Patient per Year [95% CI]	3.242 [2.855, 3.680]	3.358 [2.965, 3.802]	2.893 [2.404, 3.481]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.965 [0.808, 1.153] 0.698
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.121 [0.896, 1.402] 0.319
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.862 [0.689, 1.078] 0.192

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18h Statistical Analysis of Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	286	153		
Effect					
Treatment				0.112	
Sex				0.120	
Age group (< 65 years, >= 65 years)				0.615	
Adjusted Rate per Patient per Year [95% CI]	2.174 [1.865, 2.534]	2.652 [2.271, 3.098]	2.742 [2.212, 3.398]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.820 [0.659, 1.019] 0.074
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.793 [0.609, 1.032] 0.085
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.034 [0.793, 1.347] 0.806

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18i Statistical Analysis of Treatment Emergent Adverse Events by Region, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	320	160		
Effect					
Treatment				0.191	
Sex				0.256	
Age group (< 65 years, >= 65 years)				0.769	
Adjusted Rate per Patient per Year [95% CI]	2.726 [2.391, 3.108]	2.952 [2.590, 3.365]	2.380 [1.963, 2.885]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.923 [0.767, 1.111] 0.399
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.145 [0.907, 1.446] 0.253
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.806 [0.639, 1.017] 0.070

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.18i Statistical Analysis of Treatment Emergent Adverse Events by Region, excluding Severe Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	253	127		
Effect					
Treatment				0.157	
Sex				0.696	
Age group (< 65 years, >= 65 years)				0.467	
Adjusted Rate per Patient per Year [95% CI]	2.640 [2.271, 3.069]	3.076 [2.649, 3.572]	3.331 [2.704, 4.105]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.858 [0.694, 1.062] 0.159
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.792 [0.613, 1.025] 0.076
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.083 [0.837, 1.402] 0.544

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19a Statistical Analysis of Serious Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	450	246		
Effect					
Treatment				0.544	
Sex				0.712	
Adjusted Rate per Patient per Year [95% CI]	0.059 [0.039, 0.089]	0.044 [0.027, 0.071]	0.064 [0.037, 0.113]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.339 [0.708, 2.530] 0.369
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.916 [0.457, 1.835] 0.804
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.462 [0.697, 3.066] 0.315

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, sex

Table 21.2.19a Statistical Analysis of Serious Treatment Emergent Adverse Events by Age Group
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.091	
Sex				0.960	
Adjusted Rate per Patient per Year [95% CI]	0.069 [0.026, 0.179]	0.201 [0.107, 0.376]	0.053 [0.011, 0.263]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.341 [0.109, 1.071] 0.065
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.301 [0.199, 8.493] 0.783
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.262 [0.047, 1.477] 0.129

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, sex

Table 21.2.19b Statistical Analysis of Serious Treatment Emergent Adverse Events by Gender (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	245	103		
Effect					
Treatment				0.254	
Age group (< 65 years, >= 65 years)				0.044*	
Adjusted Rate per Patient per Year [95% CI]	0.053 [0.027, 0.103]	0.080 [0.047, 0.137]	0.028 [0.008, 0.096]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.658 [0.282, 1.538] 0.334
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.860 [0.463, 7.465] 0.382
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.354 [0.094, 1.331] 0.124

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.19b Statistical Analysis of Serious Treatment Emergent Adverse Events by Gender (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	328	184		
Effect					
Treatment				0.557	
Age group (< 65 years, >= 65 years)				0.017*	
Adjusted Rate per Patient per Year [95% CI]	0.064 [0.039, 0.105]	0.056 [0.032, 0.097]	0.089 [0.047, 0.171]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.138 [0.546, 2.372] 0.730
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.713 [0.315, 1.614] 0.417
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.596 [0.674, 3.779] 0.288

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.19c Statistical Analysis of Serious Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.304	
Age group (< 65 years, >= 65 years)				0.050*	
Adjusted Rate per Patient per Year [95% CI]	0.031 [0.012, 0.080]	0.068 [0.036, 0.129]	0.030 [0.007, 0.127]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.462 [0.153, 1.401] 0.173
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.035 [0.187, 5.732] 0.968
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.447 [0.093, 2.149] 0.315

Produced: 17 December 2020

Page 1 of 3

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19c Statistical Analysis of Serious Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.924	
Sex				0.606	
Age group (< 65 years, >= 65 years)				0.860	
Adjusted Rate per Patient per Year [95% CI]	0.058 [0.028, 0.120]	0.069 [0.034, 0.142]	0.055 [0.020, 0.155]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.842 [0.300, 2.361] 0.743
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.051 [0.302, 3.662] 0.938
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.801 [0.225, 2.845] 0.731

Produced: 17 December 2020

Page 2 of 3

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19c Statistical Analysis of Serious Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	205	102		
Effect					
Treatment				0.727	
Sex				0.807	
Age group (< 65 years, >= 65 years)				0.002**	
Adjusted Rate per Patient per Year [95% CI]	0.080 [0.045, 0.141]	0.063 [0.034, 0.117]	0.093 [0.043, 0.201]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.264 [0.551, 2.900] 0.580
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.860 [0.329, 2.245] 0.757
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.471 [0.547, 3.950] 0.444

Produced: 17 December 2020

Page 3 of 3

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19d Statistical Analysis of Serious Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	493	245		
Effect					
Treatment				0.997	
Age group (< 65 years, >= 65 years)				0.018*	
Adjusted Rate per Patient per Year [95% CI]	0.061 [0.040, 0.093]	0.062 [0.041, 0.094]	0.062 [0.034, 0.113]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.978 [0.545, 1.756] 0.942
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.987 [0.475, 2.052] 0.973
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.991 [0.478, 2.054] 0.980

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.19d Statistical Analysis of Serious Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.833	
Age group (< 65 years, >= 65 years)				0.115	
Adjusted Rate per Patient per Year [95% CI]	0.055 [0.017, 0.178]	0.086 [0.030, 0.248]	0.087 [0.021, 0.362]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.642 [0.128, 3.219] 0.590
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.635 [0.102, 3.946] 0.626
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.011 [0.164, 6.214] 0.991

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.19e Statistical Analysis of Serious Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	452	229		
Effect					
Treatment				0.653	
Sex				0.701	
Age group (< 65 years, >= 65 years)				0.004**	
Adjusted Rate per Patient per Year [95% CI]	0.051 [0.032, 0.082]	0.068 [0.045, 0.104]	0.057 [0.030, 0.109]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.746 [0.397, 1.402] 0.362
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.898 [0.403, 2.003] 0.793
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.830 [0.384, 1.797] 0.637

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19e Statistical Analysis of Serious Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	121	58		
Effect					
Treatment				0.863	
Sex				0.165	
Age group (< 65 years, >= 65 years)				0.339	
Adjusted Rate per Patient per Year [95% CI]	0.078 [0.037, 0.167]	0.060 [0.025, 0.143]	0.084 [0.028, 0.252]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.307 [0.418, 4.087] 0.646
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.929 [0.255, 3.391] 0.912
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.406 [0.347, 5.694] 0.633

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19f Statistical Analysis of Serious Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	299	283	147		
Effect					
Treatment				0.583	
Sex				0.517	
Age group (< 65 years, >= 65 years)				0.001**	
Adjusted Rate per Patient per Year [95% CI]	0.042 [0.022, 0.083]	0.063 [0.034, 0.117]	0.068 [0.029, 0.163]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.671 [0.276, 1.629] 0.377
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.620 [0.208, 1.849] 0.391
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.081 [0.362, 3.233] 0.889

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19f Statistical Analysis of Serious Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.809	
Sex				0.900	
Age group (< 65 years, >= 65 years)				0.746	
Adjusted Rate per Patient per Year [95% CI]	0.076 [0.048, 0.122]	0.061 [0.037, 0.101]	0.067 [0.033, 0.135]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.257 [0.630, 2.512] 0.516
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.138 [0.490, 2.642] 0.763
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.105 [0.467, 2.613] 0.821

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19g Statistical Analysis of Serious Treatment Emergent Adverse Events by Use of Spacer
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	139	74		
Effect					
Treatment				0.228	
Sex				0.403	
Age group (< 65 years, >= 65 years)				0.187	
Adjusted Rate per Patient per Year [95% CI]	0.047 [0.020, 0.110]	0.096 [0.051, 0.178]	0.125 [0.057, 0.272]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.488 [0.170, 1.402] 0.183
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.373 [0.117, 1.187] 0.095
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.310 [0.485, 3.535] 0.595

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19g Statistical Analysis of Serious Treatment Emergent Adverse Events by Use of Spacer
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	434	213		
Effect					
Treatment				0.637	
Sex				0.266	
Age group (< 65 years, >= 65 years)				0.005**	
Adjusted Rate per Patient per Year [95% CI]	0.063 [0.040, 0.099]	0.057 [0.035, 0.092]	0.041 [0.018, 0.089]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.101 [0.572, 2.118] 0.773
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.549 [0.628, 3.821] 0.342
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.711 [0.283, 1.787] 0.468

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19h Statistical Analysis of Serious Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.819	
Sex				0.757	
Age group (< 65 years, >= 65 years)				0.014*	
Adjusted Rate per Patient per Year [95% CI]	0.084 [0.051, 0.137]	0.083 [0.052, 0.135]	0.106 [0.055, 0.204]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.007 [0.509, 1.992] 0.984
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.790 [0.350, 1.784] 0.570
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.275 [0.562, 2.890] 0.561

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19h Statistical Analysis of Serious Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	286	153		
Effect					
Treatment				0.544	
Sex				0.760	
Age group (< 65 years, >= 65 years)				0.819	
Adjusted Rate per Patient per Year [95% CI]	0.037 [0.019, 0.074]	0.055 [0.030, 0.102]	0.029 [0.010, 0.088]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.683 [0.271, 1.723] 0.419
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.283 [0.353, 4.669] 0.705
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.532 [0.151, 1.881] 0.328

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.19i Statistical Analysis of Serious Treatment Emergent Adverse Events by Region
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	320	160		
Effect					
Treatment				0.203	
Age group (< 65 years, >= 65 years)				0.173	
Adjusted Rate per Patient per Year [95% CI]	0.077 [0.048, 0.125]	0.038 [0.020, 0.071]	0.055 [0.025, 0.119]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					2.051 [0.928, 4.531] 0.076
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.415 [0.566, 3.537] 0.458
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.450 [0.530, 3.964] 0.469

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.19i Statistical Analysis of Serious Treatment Emergent Adverse Events by Region
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	253	127		
Effect					
Treatment				0.064	
Age group (< 65 years, >= 65 years)				0.009**	
Adjusted Rate per Patient per Year [95% CI]	0.038 [0.019, 0.076]	0.102 [0.063, 0.164]	0.077 [0.036, 0.164]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.376 [0.166, 0.852] 0.019*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.497 [0.180, 1.377] 0.179
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.756 [0.309, 1.847] 0.539

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.20f Statistical Analysis of Serious Treatment Emergent Adverse Events by Degree of reversibility at screening, excluding Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	299	283	147		
Effect					
Treatment				0.403	
Sex				0.321	
Age group (< 65 years, >= 65 years)				<0.001***	
Adjusted Rate per Patient per Year [95% CI]	0.022 [0.010, 0.049]	0.042 [0.021, 0.082]	0.038 [0.014, 0.104]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.518 [0.194, 1.386] 0.190
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.570 [0.161, 2.021] 0.384
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.909 [0.271, 3.045] 0.877

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.20f Statistical Analysis of Serious Treatment Emergent Adverse Events by Degree of reversibility at screening, excluding Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.756	
Sex				0.229	
Age group (< 65 years, >= 65 years)				0.409	
Adjusted Rate per Patient per Year [95% CI]	0.049 [0.027, 0.087]	0.037 [0.020, 0.070]	0.052 [0.024, 0.114]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.307 [0.560, 3.049] 0.536
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.934 [0.352, 2.478] 0.891
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.399 [0.513, 3.820] 0.512

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.20i Statistical Analysis of Serious Treatment Emergent Adverse Events by Region, excluding Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	320	160		
Effect					
Treatment				0.399	
Sex				0.394	
Age group (< 65 years, >= 65 years)				0.218	
Adjusted Rate per Patient per Year [95% CI]	0.046 [0.026, 0.082]	0.024 [0.011, 0.051]	0.041 [0.017, 0.098]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.911 [0.740, 4.940] 0.181
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.132 [0.397, 3.230] 0.817
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.689 [0.530, 5.380] 0.375

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.20i Statistical Analysis of Serious Treatment Emergent Adverse Events by Region, excluding Asthma Exacerbations (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	253	127		
Effect					
Treatment				0.105	
Sex				0.881	
Age group (< 65 years, >= 65 years)				<0.001***	
Adjusted Rate per Patient per Year [95% CI]	0.024 [0.010, 0.053]	0.065 [0.037, 0.112]	0.049 [0.020, 0.120]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.364 [0.144, 0.925] 0.034*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.478 [0.146, 1.567] 0.223
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.762 [0.272, 2.137] 0.606

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.3

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21a Statistical Analysis of Severe Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	450	246		
Effect					
Treatment				0.095	
Sex				0.601	
Adjusted Rate per Patient per Year [95% CI]	0.070 [0.048, 0.103]	0.103 [0.074, 0.145]	0.051 [0.028, 0.094]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.677 [0.405, 1.131] 0.136
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.370 [0.665, 2.823] 0.393
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.494 [0.245, 0.996] 0.049*

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and sex

Table 21.2.21a Statistical Analysis of Severe Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.239	
Sex				0.683	
Adjusted Rate per Patient per Year [95% CI]	0.118 [0.059, 0.238]	0.186 [0.108, 0.318]	0.053 [0.012, 0.238]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.637 [0.264, 1.538] 0.316
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					2.225 [0.426, 11.63] 0.343
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.287 [0.058, 1.407] 0.124

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and sex

Table 21.2.21b Statistical Analysis of Severe Treatment Emergent Adverse Events by Gender
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	245	103		
Effect					
Treatment				0.049*	
Age group (< 65 years, >= 65 years)				0.410	
Adjusted Rate per Patient per Year [95% CI]	0.074 [0.041, 0.132]	0.138 [0.089, 0.214]	0.040 [0.014, 0.116]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.535 [0.258, 1.105] 0.091
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.847 [0.551, 6.190] 0.320
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.289 [0.092, 0.911] 0.034*

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.21b Statistical Analysis of Severe Treatment Emergent Adverse Events by Gender (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	328	184		
Effect					
Treatment				0.345	
Age group (< 65 years, >= 65 years)				0.033*	
Adjusted Rate per Patient per Year [95% CI]	0.079 [0.052, 0.119]	0.101 [0.069, 0.150]	0.058 [0.030, 0.114]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.777 [0.443, 1.364] 0.379
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.348 [0.615, 2.955] 0.456
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.576 [0.266, 1.250] 0.163

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.21c Statistical Analysis of Severe Treatment Emergent Adverse Events by BMI Class
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.027*	
Sex				0.505	
Age group (< 65 years, >= 65 years)				0.246	
Adjusted Rate per Patient per Year [95% CI]	0.053 [0.024, 0.113]	0.140 [0.085, 0.230]	0.030 [0.007, 0.128]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.374 [0.152, 0.923] 0.033*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.740 [0.339, 8.940] 0.507
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.215 [0.047, 0.992] 0.049*

Produced: 17 December 2020

Page 1 of 3

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21c Statistical Analysis of Severe Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.691	
Sex				0.765	
Age group (< 65 years, >= 65 years)				0.320	
Adjusted Rate per Patient per Year [95% CI]	0.049 [0.025, 0.098]	0.063 [0.032, 0.124]	0.037 [0.012, 0.110]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.779 [0.298, 2.035] 0.611
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.343 [0.370, 4.877] 0.654
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.580 [0.161, 2.094] 0.406

Produced: 17 December 2020

Page 2 of 3

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21c Statistical Analysis of Severe Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	205	102		
Effect					
Treatment				0.458	
Sex				0.769	
Age group (< 65 years, >= 65 years)				0.007**	
Adjusted Rate per Patient per Year [95% CI]	0.121 [0.077, 0.190]	0.139 [0.091, 0.212]	0.080 [0.038, 0.170]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.872 [0.473, 1.609] 0.662
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.508 [0.631, 3.605] 0.356
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.578 [0.245, 1.365] 0.212

Produced: 17 December 2020

Page 3 of 3

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21d Statistical Analysis of Severe Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	493	245		
Effect					
Treatment				0.005**	
Sex				0.866	
Age group (< 65 years, >= 65 years)				0.007**	
Adjusted Rate per Patient per Year [95% CI]	0.072 [0.049, 0.104]	0.118 [0.087, 0.161]	0.038 [0.019, 0.076]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.604 [0.374, 0.975] 0.039*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.876 [0.855, 4.115] 0.117
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.322 [0.151, 0.687] 0.003**

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21d Statistical Analysis of Severe Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.939	
Sex				0.954	
Age group (< 65 years, >= 65 years)				0.429	
Adjusted Rate per Patient per Year [95% CI]	0.095 [0.042, 0.216]	0.098 [0.042, 0.227]	0.119 [0.042, 0.338]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.976 [0.302, 3.159] 0.968
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.801 [0.220, 2.919] 0.736
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.219 [0.319, 4.666] 0.772

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21e Statistical Analysis of Severe Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	452	229		
Effect					
Treatment				0.015*	
Sex				0.785	
Age group (< 65 years, >= 65 years)				0.072	
Adjusted Rate per Patient per Year [95% CI]	0.072 [0.048, 0.106]	0.121 [0.087, 0.167]	0.046 [0.024, 0.090]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.593 [0.357, 0.986] 0.044*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.556 [0.717, 3.375] 0.263
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.381 [0.182, 0.799] 0.011*

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21e Statistical Analysis of Severe Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	121	58		
Effect					
Treatment				0.900	
Sex				0.939	
Age group (< 65 years, >= 65 years)				0.273	
Adjusted Rate per Patient per Year [95% CI]	0.097 [0.050, 0.187]	0.099 [0.051, 0.193]	0.074 [0.025, 0.222]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.977 [0.385, 2.480] 0.961
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.306 [0.365, 4.679] 0.681
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.748 [0.206, 2.709] 0.658

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21f Statistical Analysis of Severe Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	299	283	147		
Effect					
Treatment				0.409	
Sex				0.515	
Age group (< 65 years, >= 65 years)				0.021*	
Adjusted Rate per Patient per Year [95% CI]	0.098 [0.064, 0.151]	0.107 [0.070, 0.164]	0.060 [0.028, 0.127]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.915 [0.504, 1.662] 0.771
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.650 [0.689, 3.949] 0.261
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.555 [0.232, 1.325] 0.185

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21f Statistical Analysis of Severe Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.016*	
Sex				0.913	
Age group (< 65 years, >= 65 years)				0.999	
Adjusted Rate per Patient per Year [95% CI]	0.053 [0.030, 0.093]	0.123 [0.083, 0.183]	0.044 [0.019, 0.104]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.430 [0.215, 0.858] 0.017*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.192 [0.428, 3.322] 0.736
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.360 [0.141, 0.924] 0.034*

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21g Statistical Analysis of Severe Treatment Emergent Adverse Events by Use of Spacer
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	139	74		
Effect					
Treatment				0.035*	
Sex				0.563	
Age group (< 65 years, >= 65 years)				0.976	
Adjusted Rate per Patient per Year [95% CI]	0.063 [0.030, 0.131]	0.163 [0.102, 0.262]	0.055 [0.020, 0.153]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.386 [0.162, 0.920] 0.032*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.151 [0.327, 4.042] 0.827
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.335 [0.108, 1.037] 0.058

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21g Statistical Analysis of Severe Treatment Emergent Adverse Events by Use of Spacer
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	434	213		
Effect					
Treatment				0.199	
Sex				0.947	
Age group (< 65 years, >= 65 years)				0.014*	
Adjusted Rate per Patient per Year [95% CI]	0.081 [0.055, 0.119]	0.101 [0.070, 0.144]	0.050 [0.025, 0.099]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.803 [0.475, 1.357] 0.413
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.615 [0.740, 3.526] 0.229
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.497 [0.230, 1.074] 0.075

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment, age group and sex

Table 21.2.21h Statistical Analysis of Severe Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.137	
Age group (< 65 years, >= 65 years)				0.310	
Adjusted Rate per Patient per Year [95% CI]	0.123 [0.082, 0.184]	0.166 [0.117, 0.238]	0.078 [0.039, 0.155]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.737 [0.431, 1.262] 0.267
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.572 [0.708, 3.490] 0.266
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.469 [0.216, 1.019] 0.056

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.21h Statistical Analysis of Severe Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	286	153		
Effect					
Treatment				0.107	
Age group (< 65 years, >= 65 years)				0.671	
Adjusted Rate per Patient per Year [95% CI]	0.038 [0.020, 0.070]	0.073 [0.045, 0.117]	0.028 [0.010, 0.076]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.518 [0.238, 1.127] 0.097
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.359 [0.416, 4.441] 0.612
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.381 [0.125, 1.164] 0.090

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.21i Statistical Analysis of Severe Treatment Emergent Adverse Events by Region
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	320	160		
Effect					
Treatment				0.296	
Age group (< 65 years, >= 65 years)				0.013*	
Adjusted Rate per Patient per Year [95% CI]	0.053 [0.031, 0.091]	0.078 [0.050, 0.123]	0.040 [0.017, 0.093]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.681 [0.343, 1.354] 0.274
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.352 [0.494, 3.703] 0.557
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.504 [0.191, 1.328] 0.166

Produced: 17 December 2020

Page 1 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.21i Statistical Analysis of Severe Treatment Emergent Adverse Events by Region
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	253	127		
Effect					
Treatment				0.067	
Age group (< 65 years, >= 65 years)				0.559	
Adjusted Rate per Patient per Year [95% CI]	0.105 [0.068, 0.163]	0.164 [0.113, 0.239]	0.066 [0.031, 0.140]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.640 [0.361, 1.137] 0.128
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.594 [0.669, 3.799] 0.293
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.402 [0.173, 0.932] 0.034*

Produced: 17 December 2020

Page 2 of 2

Source: Listing 16.2.7.6

Notes: [1] Analysis is based on a negative binomial model including treatment and age group

Table 21.2.23a Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Age Group - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.019*
Sex			0.179
Age Group			0.647
Age Group Treatment Interaction			0.168

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.23b Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Gender - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.134
Age group (< 65 years, >= 65 years)			0.414
Gender			0.123
Gender Treatment Interaction			0.356

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.23c Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including BMI Class - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.058
Sex			0.175
Age group (< 65 years, >= 65 years)			0.481
BMI Class			0.059
BMI Class Treatment Interaction			0.326

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and BMI Class

Table 21.2.23d Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Smoking Status - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.617
Sex			0.153
Age group (< 65 years, >= 65 years)			0.440
Smoking Status			0.644
Smoking Status Treatment Interaction			0.214

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.23e Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Number of Exacerbation in the Previous year - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.038*
Sex			0.200
Age group (< 65 years, >= 65 years)			0.399
Number of Exacerbation in the Previous year			0.283
Number of Exacerbation in the Previous year Treatment Interaction			0.410

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.23f Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Degree of reversibility at screening - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	570	287	
Effect			
Treatment			0.057
Sex			0.138
Age group (< 65 years, >= 65 years)			0.526
Degree of reversibility at screening			0.550
Degree of reversibility at screening Treatment Interaction			0.394

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.23g Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Use of Spacer - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.062
Sex			0.206
Age group (< 65 years, >= 65 years)			0.399
Use of Spacer			0.062
Use of Spacer Treatment Interaction			0.593

Produced: 17 December 2020 Page 1 of 1
 Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8
 Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.23h Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.059
Sex			0.253
Age group (< 65 years, >= 65 years)			0.250
Relevant Concomitant Cardiovascular Diseases			0.104
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.454

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.23i Statistical Analysis of Infections and infestations Treatment Emergent Adverse Events including Region - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.054
Sex			0.194
Age group (< 65 years, >= 65 years)			0.387
Region			0.166
Region Treatment Interaction			0.588

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.24a Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Age Group - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.005**
Sex			0.475
Age Group			0.182
Age Group Treatment Interaction			0.010*

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.24b Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Gender - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.315
Age group (< 65 years, >= 65 years)			0.208
Gender			0.357
Gender Treatment Interaction			0.379

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.24c Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including BMI Class - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.152
BMI Class			0.422
BMI Class Treatment Interaction			0.818

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, BMI Class

Table 21.2.24d Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Smoking Status - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.828
Sex			0.538
Age group (< 65 years, >= 65 years)			0.208
Smoking Status			0.443
Smoking Status Treatment Interaction			0.399

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.24e Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Number of Exacerbation in the Previous year - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.201
Sex			0.421
Age group (< 65 years, >= 65 years)			0.210
Number of Exacerbation in the Previous year			0.449
Number of Exacerbation in the Previous year Treatment Interaction			0.780

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.24f Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Degree of reversibility at screening - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	570	287	
Effect			
Treatment			0.153
Degree of reversibility at screening			0.652
Degree of reversibility at screening Treatment Interaction			0.004**

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, Degree of reversibility at screening

Table 21.2.24g Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Use of Spacer - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.146
Sex			0.454
Age group (< 65 years, >= 65 years)			0.219
Use of Spacer			0.563
Use of Spacer Treatment Interaction			0.682

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.24h Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Relevant Concomitant Cardiovascular Diseases - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.118
Sex			0.471
Age group (< 65 years, >= 65 years)			0.298
Relevant Concomitant Cardiovascular Diseases			0.736
Relevant Concomitant Cardiovascular Diseases Treatment Interaction			0.184

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.24i Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events including Region - Interaction Test (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects
Number of Patients Included in Model	571	287	
Effect			
Treatment			0.188
Sex			0.457
Age group (< 65 years, >= 65 years)			0.198
Region			0.049*
Region Treatment Interaction			0.473

Produced: 17 December 2020

Page 1 of 1

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.25a Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	450	246		
Effect					
Treatment				0.137	
Sex				0.117	
Adjusted Rate per Patient per Year [95% CI]	0.403 [0.336, 0.484]	0.517 [0.435, 0.615]	0.489 [0.385, 0.622]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.780 [0.606, 1.003] 0.052
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.825 [0.611, 1.115] 0.210
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.945 [0.703, 1.271] 0.708

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, sex

Table 21.2.25a Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.029*	
Sex				0.461	
Adjusted Rate per Patient per Year [95% CI]	0.274 [0.177, 0.424]	0.536 [0.392, 0.731]	0.580 [0.343, 0.981]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.512 [0.300, 0.874] 0.014*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.473 [0.239, 0.935] 0.031*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.083 [0.588, 1.995] 0.798

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, sex

Table 21.2.25b Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Gender (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	245	103		
Effect					
Treatment				0.345	
Age group (< 65 years, >= 65 years)				0.821	
Adjusted Rate per Patient per Year [95% CI]	0.360 [0.272, 0.476]	0.471 [0.370, 0.599]	0.392 [0.265, 0.580]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.764 [0.528, 1.106] 0.154
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.917 [0.567, 1.483] 0.724
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.833 [0.526, 1.319] 0.436

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.25b Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Gender (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	328	184		
Effect					
Treatment				0.032*	
Age group (< 65 years, >= 65 years)				0.746	
Adjusted Rate per Patient per Year [95% CI]	0.397 [0.323, 0.489]	0.559 [0.459, 0.681]	0.572 [0.439, 0.745]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.711 [0.533, 0.947] 0.020*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.695 [0.496, 0.972] 0.034*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.023 [0.736, 1.423] 0.892

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.25c Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.135	
Sex				0.710	
Age group (< 65 years, >= 65 years)				0.508	
Adjusted Rate per Patient per Year [95% CI]	0.384 [0.278, 0.530]	0.507 [0.384, 0.671]	0.640 [0.430, 0.952]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.757 [0.494, 1.159] 0.201
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.600 [0.360, 1.000] 0.050
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.261 [0.776, 2.051] 0.349

Produced: 17 December 2020

Page 1 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.25c Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.082	
Sex				0.171	
Age group (< 65 years, >= 65 years)				0.388	
Adjusted Rate per Patient per Year [95% CI]	0.344 [0.261, 0.453]	0.503 [0.390, 0.649]	0.336 [0.227, 0.498]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.683 [0.470, 0.994] 0.046*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.022 [0.635, 1.647] 0.927
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.668 [0.419, 1.067] 0.091

Produced: 17 December 2020

Page 2 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.25c Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	205	102		
Effect					
Treatment				0.267	
Sex				0.064	
Age group (< 65 years, >= 65 years)				0.496	
Adjusted Rate per Patient per Year [95% CI]	0.418 [0.316, 0.551]	0.542 [0.419, 0.701]	0.578 [0.404, 0.825]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.771 [0.528, 1.125] 0.177
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.723 [0.461, 1.134] 0.157
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.066 [0.687, 1.655] 0.776

Produced: 17 December 2020

Page 3 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.25d Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	493	245		
Effect					
Treatment				0.013*	
Sex				0.500	
Age group (< 65 years, >= 65 years)				0.791	
Adjusted Rate per Patient per Year [95% CI]	0.363 [0.302, 0.436]	0.509 [0.431, 0.600]	0.517 [0.409, 0.654]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.714 [0.557, 0.914] 0.008**
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.703 [0.522, 0.946] 0.020*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.016 [0.762, 1.354] 0.914

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.25d Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.515	
Sex				0.002**	
Age group (< 65 years, >= 65 years)				0.901	
Adjusted Rate per Patient per Year [95% CI]	0.454 [0.303, 0.679]	0.573 [0.390, 0.844]	0.390 [0.215, 0.707]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.791 [0.453, 1.381] 0.409
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.162 [0.573, 2.358] 0.677
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.680 [0.335, 1.382] 0.287

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Smoking Status

Table 21.2.25e Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	452	229		
Effect					
Treatment				0.080	
Sex				0.278	
Age group (< 65 years, >= 65 years)				0.633	
Adjusted Rate per Patient per Year [95% CI]	0.376 [0.310, 0.457]	0.507 [0.425, 0.605]	0.466 [0.360, 0.602]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.742 [0.570, 0.966] 0.026*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.808 [0.586, 1.114] 0.194
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.918 [0.672, 1.254] 0.591

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.25e Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	121	58		
Effect					
Treatment				0.131	
Sex				0.111	
Age group (< 65 years, >= 65 years)				0.901	
Adjusted Rate per Patient per Year [95% CI]	0.396 [0.286, 0.549]	0.577 [0.428, 0.779]	0.637 [0.420, 0.968]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.686 [0.441, 1.068] 0.095
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.622 [0.367, 1.054] 0.078
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.103 [0.660, 1.844] 0.707

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Number of Exacerbation in the Previous year

Table 21.2.25f Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Degree of reversibility at screening
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL Number of Patients Included in Model	299	283	147		
Effect					
Treatment				0.019*	
Sex				0.024*	
Age group (< 65 years, >= 65 years)				0.362	
Adjusted Rate per Patient per Year [95% CI]	0.344 [0.271, 0.436]	0.527 [0.425, 0.653]	0.520 [0.386, 0.702]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.653 [0.474, 0.899] 0.009**
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.661 [0.452, 0.968] 0.033*
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.987 [0.682, 1.429] 0.946

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.25f Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Degree of reversibility at screening
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.405	
Sex				0.576	
Age group (< 65 years, >= 65 years)				0.166	
Adjusted Rate per Patient per Year [95% CI]	0.413 [0.326, 0.524]	0.513 [0.413, 0.636]	0.489 [0.355, 0.674]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.806 [0.585, 1.111] 0.188
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.845 [0.567, 1.259] 0.407
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.954 [0.649, 1.404] 0.812

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Degree of reversibility at screening

Table 21.2.25g Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Use of Spacer (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	139	74		
Effect					
Treatment				0.097	
Sex				0.654	
Age group (< 65 years, >= 65 years)				0.858	
Adjusted Rate per Patient per Year [95% CI]	0.448 [0.326, 0.615]	0.693 [0.530, 0.905]	0.665 [0.460, 0.962]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.647 [0.427, 0.979] 0.040*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.674 [0.415, 1.096] 0.112
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.960 [0.608, 1.516] 0.860

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.25g Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Use of Spacer (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	434	213		
Effect					
Treatment				0.148	
Sex				0.144	
Age group (< 65 years, >= 65 years)				0.494	
Adjusted Rate per Patient per Year [95% CI]	0.360 [0.296, 0.439]	0.468 [0.389, 0.563]	0.444 [0.339, 0.581]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.770 [0.588, 1.008] 0.057
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.811 [0.582, 1.132] 0.218
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.949 [0.684, 1.315] 0.751

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Use of Spacer

Table 21.2.25h Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.054	
Sex				0.587	
Age group (< 65 years, >= 65 years)				0.338	
Adjusted Rate per Patient per Year [95% CI]	0.399 [0.314, 0.507]	0.570 [0.461, 0.704]	0.584 [0.430, 0.794]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.700 [0.508, 0.965] 0.029*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.683 [0.463, 1.007] 0.054
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.025 [0.705, 1.492] 0.896

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.25h Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	286	153		
Effect					
Treatment				0.257	
Sex				0.087	
Age group (< 65 years, >= 65 years)				0.871	
Adjusted Rate per Patient per Year [95% CI]	0.363 [0.287, 0.458]	0.475 [0.381, 0.591]	0.425 [0.311, 0.582]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.765 [0.555, 1.053] 0.100
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.853 [0.577, 1.261] 0.426
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.896 [0.611, 1.314] 0.575

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Relevant Concomitant Cardiovascular Diseases

Table 21.2.25i Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Region (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	320	160		
Effect					
Treatment				0.134	
Sex				0.583	
Age group (< 65 years, >= 65 years)				0.372	
Adjusted Rate per Patient per Year [95% CI]	0.363 [0.286, 0.459]	0.502 [0.405, 0.622]	0.440 [0.321, 0.605]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.722 [0.525, 0.993] 0.045*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.823 [0.555, 1.221] 0.333
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.877 [0.599, 1.286] 0.502

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.25i Statistical Analysis of Infections and Infestations Treatment Emergent Adverse Events by Region (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	253	127		
Effect					
Treatment				0.112	
Sex				0.051	
Age group (< 65 years, >= 65 years)				0.776	
Adjusted Rate per Patient per Year [95% CI]	0.404 [0.319, 0.512]	0.543 [0.437, 0.675]	0.570 [0.422, 0.771]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.744 [0.539, 1.026] 0.072
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.709 [0.483, 1.038] 0.077
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.050 [0.724, 1.523] 0.797

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex and Region

Table 21.2.26a Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: <65 years old					
Number of Patients Included in Model	473	450	246		
Effect					
Treatment				0.319	
Sex				0.159	
Adjusted Rate per Patient per Year [95% CI]	0.114 [0.084, 0.155]	0.156 [0.118, 0.207]	0.125 [0.083, 0.189]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.732 [0.483, 1.108] 0.140
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.913 [0.547, 1.524] 0.727
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.802 [0.487, 1.319] 0.384

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, sex

Table 21.2.26a Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Age Group (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Age Group: >= 65 years old					
Number of Patients Included in Model	98	123	41		
Effect					
Treatment				0.013*	
Sex				0.234	
Adjusted Rate per Patient per Year [95% CI]	0.020 [0.005, 0.081]	0.101 [0.056, 0.181]	0.204 [0.098, 0.425]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.199 [0.044, 0.899] 0.036*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.098 [0.020, 0.472] 0.004**
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					2.025 [0.800, 5.129] 0.137

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, sex

Table 21.2.26b Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Gender (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Male					
Number of Patients Included in Model	212	245	103		
Effect					
Treatment				0.940	
Age group (< 65 years, >= 65 years)				0.159	
Adjusted Rate per Patient per Year [95% CI]	0.094 [0.059, 0.150]	0.105 [0.069, 0.159]	0.097 [0.050, 0.186]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.899 [0.487, 1.661] 0.734
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.974 [0.441, 2.149] 0.948
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.923 [0.429, 1.985] 0.838

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.26b Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Gender (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Gender: Female					
Number of Patients Included in Model	359	328	184		
Effect					
Treatment				0.065	
Age group (< 65 years, >= 65 years)				0.289	
Adjusted Rate per Patient per Year [95% CI]	0.098 [0.067, 0.144]	0.175 [0.126, 0.242]	0.161 [0.103, 0.252]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.564 [0.342, 0.928] 0.024*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.612 [0.340, 1.100] 0.101
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.921 [0.529, 1.605] 0.772

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group

Table 21.2.26c Statistical Analysis of Nsopharyngitis Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: < 25					
Number of Patients Included in Model	150	163	73		
Effect					
Treatment				0.603	
Sex				0.803	
Age group (< 65 years, >= 65 years)				0.714	
Adjusted Rate per Patient per Year [95% CI]	0.132 [0.082, 0.214]	0.107 [0.065, 0.176]	0.161 [0.085, 0.306]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					1.239 [0.618, 2.482] 0.546
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.821 [0.368, 1.831] 0.629
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.509 [0.668, 3.408] 0.322

Produced: 17 December 2020

Page 1 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26c Statistical Analysis of Nsopharyngitis Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: [25-30]					
Number of Patients Included in Model	217	205	112		
Effect					
Treatment				0.126	
Sex				0.065	
Age group (< 65 years, >= 65 years)				0.077	
Adjusted Rate per Patient per Year [95% CI]	0.081 [0.049, 0.134]	0.154 [0.103, 0.231]	0.106 [0.056, 0.198]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.527 [0.282, 0.986] 0.045*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.770 [0.350, 1.695] 0.516
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.685 [0.327, 1.432] 0.314

Produced: 17 December 2020

Page 2 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26c Statistical Analysis of Nsopharyngitis Treatment Emergent Adverse Events by BMI Class (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
BMI Class: >=30					
Number of Patients Included in Model	204	205	102		
Effect					
Treatment				0.187	
Sex				0.219	
Age group (< 65 years, >= 65 years)				0.468	
Adjusted Rate per Patient per Year [95% CI]	0.082 [0.047, 0.143]	0.158 [0.101, 0.247]	0.140 [0.074, 0.266]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.521 [0.255, 1.065] 0.074
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.589 [0.255, 1.362] 0.216
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.885 [0.404, 1.937] 0.760

Produced: 17 December 2020

Page 3 of 3

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26d Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Non smoker					
Number of Patients Included in Model	488	493	245		
Effect					
Treatment				0.156	
Sex				0.414	
Age group (< 65 years, >= 65 years)				0.281	
Adjusted Rate per Patient per Year [95% CI]	0.097 [0.071, 0.134]	0.140 [0.106, 0.184]	0.147 [0.100, 0.216]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.696 [0.458, 1.060] 0.091
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.663 [0.404, 1.088] 0.104
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.051 [0.655, 1.685] 0.837

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26d Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Smoking Status (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Smoking Status: Ex-smoker					
Number of Patients Included in Model	83	80	42		
Effect					
Treatment				0.268	
Sex				0.030*	
Age group (< 65 years, >= 65 years)				0.136	
Adjusted Rate per Patient per Year [95% CI]	0.069 [0.029, 0.166]	0.140 [0.068, 0.288]	0.057 [0.016, 0.210]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.493 [0.178, 1.364] 0.173
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.209 [0.280, 5.213] 0.799
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.407 [0.100, 1.658] 0.210

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26e Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: 1					
Number of Patients Included in Model	439	452	229		
Effect					
Treatment				0.343	
Sex				0.344	
Age group (< 65 years, >= 65 years)				0.065	
Adjusted Rate per Patient per Year [95% CI]	0.101 [0.073, 0.141]	0.137 [0.102, 0.184]	0.138 [0.091, 0.208]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.739 [0.475, 1.150] 0.180
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.736 [0.435, 1.246] 0.253
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.004 [0.606, 1.666] 0.986

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26e Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Number of Exacerbation in the Previous year
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Number of Exacerbation in the Previous year: > 1					
Number of Patients Included in Model	132	121	58		
Effect					
Treatment				0.136	
Sex				0.039*	
Age group (< 65 years, >= 65 years)				0.931	
Adjusted Rate per Patient per Year [95% CI]	0.070 [0.036, 0.139]	0.164 [0.098, 0.274]	0.111 [0.048, 0.256]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.429 [0.187, 0.986] 0.046*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.633 [0.221, 1.812] 0.395
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.678 [0.259, 1.771] 0.428

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26f Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): (200-400] mL					
Number of Patients Included in Model	299	283	147		
Effect					
Treatment				0.006**	
Sex				0.266	
Age group (< 65 years, >= 65 years)				0.163	
Adjusted Rate per Patient per Year [95% CI]	0.060 [0.037, 0.097]	0.129 [0.090, 0.185]	0.167 [0.107, 0.260]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.463 [0.254, 0.844] 0.012*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.357 [0.187, 0.684] 0.002**
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.296 [0.735, 2.284] 0.371

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26f Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Degree of reversibility at screening (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Degree of reversibility at screening (delta FEV1): > 400 mL					
Number of Patients Included in Model	271	290	140		
Effect					
Treatment				0.375	
Sex				0.109	
Age group (< 65 years, >= 65 years)				0.609	
Adjusted Rate per Patient per Year [95% CI]	0.136 [0.092, 0.201]	0.159 [0.112, 0.227]	0.096 [0.052, 0.178]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.854 [0.505, 1.445] 0.556
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					1.419 [0.683, 2.945] 0.348
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.602 [0.295, 1.229] 0.163

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26g Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Use of Spacer (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: Yes					
Number of Patients Included in Model	129	139	74		
Effect					
Treatment				0.108	
Sex				0.435	
Age group (< 65 years, >= 65 years)				0.262	
Adjusted Rate per Patient per Year [95% CI]	0.077 [0.039, 0.151]	0.186 [0.116, 0.299]	0.129 [0.062, 0.266]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.412 [0.180, 0.941] 0.035*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.597 [0.223, 1.599] 0.305
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.690 [0.291, 1.637] 0.400

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26g Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Use of Spacer
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Use of Spacer: No					
Number of Patients Included in Model	442	434	213		
Effect					
Treatment				0.426	
Sex				0.145	
Age group (< 65 years, >= 65 years)				0.201	
Adjusted Rate per Patient per Year [95% CI]	0.101 [0.073, 0.141]	0.131 [0.097, 0.178]	0.136 [0.088, 0.209]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.770 [0.492, 1.203] 0.251
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.746 [0.435, 1.278] 0.285
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.032 [0.611, 1.745] 0.906

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26h Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: Yes					
Number of Patients Included in Model	273	287	134		
Effect					
Treatment				0.041*	
Sex				0.944	
Age group (< 65 years, >= 65 years)				0.101	
Adjusted Rate per Patient per Year [95% CI]	0.073 [0.045, 0.118]	0.152 [0.106, 0.218]	0.148 [0.087, 0.250]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.478 [0.262, 0.873] 0.016*
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.494 [0.243, 1.004] 0.051
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.969 [0.512, 1.832] 0.922

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26h Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Relevant Concomitant Cardiovascular Diseases
(Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Relevant Concomitant Cardiovascular Diseases: No					
Number of Patients Included in Model	298	286	153		
Effect					
Treatment				0.849	
Sex				0.023*	
Age group (< 65 years, >= 65 years)				0.609	
Adjusted Rate per Patient per Year [95% CI]	0.115 [0.079, 0.167]	0.133 [0.093, 0.192]	0.122 [0.072, 0.205]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.860 [0.512, 1.445] 0.570
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.942 [0.497, 1.784] 0.854
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.914 [0.485, 1.721] 0.780

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26i Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Region (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Europe					
Number of Patients Included in Model	319	320	160		
Effect					
Treatment				0.256	
Sex				0.076	
Age group (< 65 years, >= 65 years)				0.078	
Adjusted Rate per Patient per Year [95% CI]	0.079 [0.051, 0.122]	0.126 [0.087, 0.181]	0.094 [0.053, 0.167]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.630 [0.361, 1.100] 0.104
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.842 [0.413, 1.716] 0.636
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					0.748 [0.380, 1.474] 0.402

Produced: 17 December 2020

Page 1 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex

Table 21.2.26i Statistical Analysis of Nasopharyngitis Treatment Emergent Adverse Events by Region (Safety Population)

	CHF 5993 pMDI HS (N=571)	CHF 1535 pMDI HS (N=573)	CHF 1535 pMDI HS + Tiotropium (N=287)	p-value for Effects	Adjusted Rate Ratio [95% CI] p-value
Region: Rest of World					
Number of Patients Included in Model	252	253	127		
Effect					
Treatment				0.242	
Sex				0.514	
Age group (< 65 years, >= 65 years)				0.491	
Adjusted Rate per Patient per Year [95% CI]	0.113 [0.075, 0.170]	0.166 [0.116, 0.237]	0.185 [0.114, 0.299]		
CHF 5993 pMDI HS / CHF 1535 pMDI HS					0.682 [0.396, 1.176] 0.168
CHF 5993 pMDI HS / CHF 1535 pMDI HS + Tiotropium					0.612 [0.325, 1.152] 0.128
CHF 1535 pMDI HS + Tiotropium / CHF 1535 pMDI HS					1.114 [0.611, 2.030] 0.725

Produced: 17 December 2020

Page 2 of 2

Source: Listings 16.2.7.2, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7 and 16.2.7.8

Notes: [1] Analysis is based on a negative binomial model including treatment, age group, sex