# Resolution

Gemeinsamer Bundesausschuss

## of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Volanesorsen

of 20 February 2020

At its session on 20 February 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

**I. Annex XII shall be amended in alphabetical order to include the active ingredient volanesorsen as follows:**

**Volanesorsen**

Resolution of: 20 February 2020
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

**Therapeutic indication (according to the marketing authorisation of 15 August 2019):**

Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

## 1. Extent of the additional benefit and the significance of the proof

Volanesorsen is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure.

Adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

**Extent of the additional benefit of volanesorsen indicating the significance of the evidence:**

Hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

**Study results according to endpoints:**[1]

[1] Data from the dossier evaluation by the G-BA (published on 15 November 2019) unless otherwise indicated.

APPROACH study: randomised, blinded, controlled Phase III study, volanesorsen vs placebo

**Mortality**

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *Effect estimator p value* |
| Mortality | 33 | 0 | 33 | 0 | - |
| N: Number of patients evaluated; n: number of patients with (at least one) event | | | | | |

**Morbidity**

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *Median (P25, P75)* | *N* | *Median (P25, P75)* | *Median difference[1] [95% CI][1] p value[2]* |
| Change in the percentage of fasting triglyceride values (unit: mg/dl) | | | | | |
| Baseline[2] | 33 | 1891 (1328, 3098) | 33 | 2012 (1130, 3026) | - |
| Percentage change in fasting TG from month 3[3] to baseline | 33 | −77.8 (−87.6, −68.4) | 33 | 11.2 (−14.6, 23.4) | −80.9 [−98.2; −65.8] < 0.0001 |
| Percentage change in fasting TG from month 6[4] to baseline | 33 | −68.4 (−84.8, −42.3) | 33 | 17.1 (−10.8, 35.2) | −76.6 [−95.4; −57.7] < 0.0001 |
| Percentage change in fasting TG from month 12[5] to baseline | 33 | −59.6 (−72.4, −30.8) | 33 | −2.7 (−28.3, 36.1) | −47.8 [−69.2; −26.4] < 0.0001 |

1. Median difference and p value are based on 5,000 test results of the Wilcoxon rank-sum test with Hodges-Lehman procedure (from 5,000 data sets imputed by bootstrap). Each Wilcoxon ranked test is performed for the percentage change from baseline for the study arm that received volanesorsen or for the study arm that received placebo. The 95% CI are modified using the Hodges-Lehman procedure.
2. Average of the values for day 1 before dosing and the previous value; if one of these values is missing, the other value is defined as baseline value.
3. Endpoint defined as average of week 12 (day 78) and 13 (day 85). There were no missing values for at month 3.
4. Endpoint defined as average of week 25 (day 169) and 26 (day 176) [volanesorsen: n = 29; placebo = 31]. Missing data is calculated using the bootstrap method to create 5,000 records. If the endpoint is missing, the median of the imputed data sets is used for each patient in the summary.
5. Endpoint defined as average of week 50 (day 344)/51 (day 351) and 52 (day 358) [volanesorsen: n = 27; placebo = 32]. Missing data is calculated using the bootstrap method to create 5,000 records. If the endpoint is missing, the median of the imputed data sets is used for each patient in the summary.

CI: confidence interval; N: number of patients evaluated; TG: triglyceride values; vs: versus

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *n (%)* | *N* | *n (%)* | *Effect estimator p value* |
| Independently confirmed pancreatitis | | | | | |
| Frequency of independently confirmed pancreatitis | 33 | 1 (3.0) | 33 | 3 (9.1) | –[1] |
| | *N* | *MV (SD)* | *N* | *MV (SD)* | *Effect estimator p value* |
| Rate of independently confirmed pancreatitis per year[2] | | 0.09 (0.53) | | 0.11 (0.39) | –[3] |
| | | | | | |

1. Because of differences in the median duration of treatment (min; max) in the 52-week treatment phase between the treatment groups (placebo: 358 days (163; 379) vs volanesorsen: 346 days (57; 372)), the calculation of an effect estimate not adjusted for treatment time is strongly biased and is therefore not reported.
2. Calculated as: (number of episodes during the treatment phase)/(date of last dose − date of first dose + 28) × 365.25.
3. The comparison based on a two-sample T-test submitted by the pharmaceutical company is not considered adequate and is therefore not reported because the data available do not allow a normal distribution to be assumed.

MV: mean value; N: number of patients evaluated; n: number of patients with (at least one) event; SD: standard deviation; vs: versus

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *LS mean [95% CI]* | *N* | *LS mean [95% CI]* | *LS mean [95% CI][1] p value[1]* |
| EQ-5D-VAS | | | | | |
| Baseline *MV (SD)* | 24 | 87.75 (10.45) | 33 | 88.12 (8.40) | |
| Change at week 13 | 24 | −5.77 [−11.20; −0.34] | 25 | −1.74 [−7.06; 3.58] | −4.03 [−11.65; 3.59] 0.2920 |

1. LS mean, confidence intervals, and p value were calculated using the ANCOVA model. In the model, the baseline value as a dependent variable, treatment, age, and baseline results were considered as covariates.

ANCOVA: covariance analysis; EQ-5D-VAS: Visual analogue scale of the EuroQol 5-dimensional questionnaire; CI: confidence interval; LS mean: least squares mean; MV mean value; N: number of patients evaluated; SD: standard deviation; vs: versus

**Health-related quality of life**

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *LS mean [95% CI]* | *N* | *LS mean [95% CI]* | *LS mean [95% CI][1] p value[1]* |
| **SF-36** | | | | | |
| Physical component score (PCS)[2] | | | | | |
| Baseline, *MV (SD)* | 24 | 54.20 (7.25) | 26 | 54.12 (4.89) | - |
| Change at week 13 | 24 | −1.22 [−3.88; 1.44] | 25 | −0.56 [−3.17; 2.05] | −0.66 [−4.40; 3.08] 0.7231 |
| Mental component score (MCS)[2] | | | | | |
| Baseline, *MV (SD)* | 24 | 51.99 (10.32) | 26 | 53.58 (6.00) | - |
| Change at week 13 | 24 | −1.86 [−5.66; 1.93] | 25 | −0.24 [−3.97; 3.48] | −1.62 [−6.97; 3.73] 0.5449 |
| Physical functioning | | | | | |
| Baseline, *MV (SD)* | 24 | 55.63 (3.61) | 26 | 55.63 (3.90) | - |
| Change at week 13 | 24 | −1.31 [−3.79; 1.17] | 25 | −1.50 (−3.93; 0.93) | 0.19 [−3.29; 3.67] 0.9130 |
| Physical role function | | | | | |
| Baseline, *MV (SD)* | 24 | 52.48 (7.07) | 26 | 53.88 (4.23) | - |
| Change at week 13 | 24 | 0.23 [−2.86; 3.31] | 25 | −0.94 [−3.96; 2.09] | 1.17 [−3.18; 5.51] 0.5919 |
| Physical pain | | | | | |
| Baseline, *MV (SD)* | 24 | 55.08 (12.42) | 26 | 55.53 (6.88) | - |
| Change at week 13 | 24 | 0.37 [−2.94; 3.68] | 25 | 0.47 [−2.78; 3.71] | −0.09 [−4.74; 4.55] 0.9683 |
| General health perception | | | | | |
| Baseline, *MV (SD)* | 24 | 51.18 (11.23) | 26 | 49.46 (9.72) | - |
| Change at week 13 | 24 | −0.03 [−2.76; 2.71] | 25 | 2.21 [−0.46; 4.89] | −2.24 [−6.07; 1.60] 0.2460 |

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *LS mean [95% CI]* | *N* | *LS mean [95% CI]* | *LS mean [95% CI][1] p value[1]* |
| Vitality | | | | | |
| Baseline, *MV (SD)* | 24 | 55.07 (11.44) | 26 | 57.06 (7.85) | - |
| Change at week 13 | 24 | 0.58 [−2.36; 3.52] | 25 | −0.32 [−3.20; 2.56] | 0.90 [−3.23; 5.03] 0.6627 |
| Social role function | | | | | |
| Baseline, *MV (SD)* | 24 | 51.70 (8.66) | 26 | 53.87 (5.07) | - |
| Change at week 13 | 24 | 1.01 [−2.04; 4.05] | 25 | −0.56 [−3.54; 2.42] | 1.57 [−2.72; 5.86] 0.4656 |
| Emotional role function | | | | | |
| Baseline, *MV (SD)* | 24 | 52.98 (7.11) | 26 | 53.76 (4.38) | - |
| Change at week 13 | 24 | 0.17 [−2.55; 2.90] | 25 | −1.56 [−4.23; 1.11] | 1.73 [−2.10; 5.56] 0.3667 |
| Mental well-being | | | | | |
| Baseline, *MV (SD)* | 24 | 52.39 (9.97) | 26 | 53.18 (7.70) | - |
| Change at week 13 | 24 | 0.46 [−2.87; 3.79] | 25 | 0.40 [−2.86; 3.66] | 0.05 [−4.62; 4.73] 0.9814 |

1. LS mean, confidence intervals, and p value were calculated using the ANCOVA model. In the model, the baseline value as a dependent variable, treatment, age, and baseline results were considered as covariates.
2. Post hoc analysis Data from Module 4 of the dossier.

ANCOVA: analysis of covariance; CI: confidence interval; MV: mean; LS mean: least squares mean; N number of patients evaluated; SD: standard deviation; SF-36: 36-Item Short Form Health Survey (questionnaire), vs: versus

**Side effects**

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *Effect estimator p value* |
| **Total rates[1]** | | | | | |
| Adverse events (AE) | | | | | |
| | 33 | 32 (97.0) | 33 | 30 (90.9) | –[2] |
| Severe AE | | | | | |
| | 33 | 5 (15.2) | 33 | 1 (3.0) | –[2] |

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *Effect estimator p value* |
| Serious adverse events (SAE) | | | | | |
| | 33 | 6 (18.2) | 33 | 2 (6.1) | –[2] |
| Therapy discontinuations because of AE[3] | | | | | |
| | 33 | 9 (27.3) | 33 | 0 | –[2] |
| AE leading to death | | | | | |
| | 33 | 0 | 33 | 0 | n.a. |
| **SAE with incidence ≥ 10%** | | | | | |
| MedDRA System Organ Class[4, 5]<br>Preferred Term[4, 5]<br>Representation at ≥ 10% difference between treatment arms | | | | | |
| **General disorders and administration site conditions** | 33 | 29 (87.9) | 33 | 15 (45.5) | –[2] |
| Erythema at the injection site | 33 | 25 (75.8) | 33 | 1 (3.0) | no data available |
| Pain at the injection site | 33 | 15 (45.5) | 33 | 3 (9.1) | no data available |
| Pruritus at the injection site | 33 | 8 (24.2) | 33 | 0 | No data available |
| Fatigue | 33 | 7 (21.2) | 33 | 3 (9.1) | no data available |
| Discolouration of the injection site | 33 | 7 (21.2) | 33 | 0 | No data available |
| Hardening of the injection site | 33 | 7 (21.2) | 33 | 0 | No data available |
| Swelling at the injection site | 33 | 7 (21.2) | 33 | 2 (6.1) | no data available |
| Haematoma at the injection site | 33 | 5 (15.2) | 33 | 0 | No data available |
| Oedema at the injection site | 33 | 5 (15.2) | 33 | 0 | No data available |
| Reaction at the injection site | 33 | 4 (12.1) | 33 | 0 | No data available |
| Nausea | 33 | 6 (18.2) | 33 | 2 (6.1) | no data available |
| **Skin and subcutaneous tissue disorders** | 33 | 18 (54.5) | 33 | 6 (18.2) | –[2] |

| Endpoint | Volanesorsen | | Placebo | | Volanesorsen vs placebo |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *Effect estimator p value* |
| Petechiae | 33 | 4 (12.1) | 33 | 0 | No data available |
| **Investigations** | 33 | 16 (48.5) | 33 | 5 (15.2) | –[2] |
| Reduced thrombocyte count | 33 | 11 (33.3) | 33 | 1 (3.0) | no data available |
| **Nervous system disorders** | 33 | 14 (42.4) | 33 | 7 (21.2) | –[2] |
| Myalgia | 33 | 5 (15.2) | 33 | 1 (3.0) | no data available |
| Arthralgia | 33 | 4 (12.1) | 33 | 0 | No data available |
| **Blood and lymphatic system disorders** | 33 | 10 (30.3) | 33 | 2 (6.1) | –[2] |
| Thrombocytopoenia | 33 | 4 (12.1) | 33 | 0 | No data available |
| Nosebleeds | 33 | 5 (15.2) | 33 | 0 | No data available |
| **Metabolism and nutrition disorders** | 33 | 6 (18.2) | 33 | 2 (6.1) | –[2] |
| Diabetes mellitus | 33 | 4 (12.1) | 33 | 0 | No data available |
| **(Pre-)specified AE of special interest (AESI)** | | | | | |
| Bleedings[6] | 33 | 16 (48.5) | 33 | 4 (12.1) | –[2] |

1. Post hoc evaluation without events recorded as patient-relevant endpoints in the morbidity category abdominal pain and (acute) pancreatitis. An AE was defined as an event that begins or worsens with or after the first dose of the study medication.
2. Because of differences in the median duration of treatment (min; max) in the 52-week treatment phase between the treatment groups (placebo: 358 days (163; 379) vs volanesorsen: 346 days (57; 372)), the calculation of an effect estimate not adjusted for treatment time is strongly biased and is therefore not reported.
3. Reasons for the discontinuation of the study medication in the volanesorsen arm were: General disorders and administration site conditions (including fatigue, chills (3 patients), reduced thrombocyte count (3 patients), thrombocytopenia (2 patients), skin and subcutaneous tissue disorders (erythema, hyperhidrosis (2 patients)). One patient had two of the aforementioned reasons.
4. In the case of several events of a study participant in a given system organ class or preferred term, this was counted as a single event in the system organ class or preferred term.
5. An AE was defined as an event that begins or worsens with or after the first dose of the study medication.
6. Bleedings were recorded as bleedings (SMQ) in accordance with MedDRA (Version 19.1): 45 bleeding events were reported in 16 patients (49%) in the volanesorsen group and five bleeding events in four patients (12%) in the placebo group. In total, 20 (40%) of the 50 bleeding events were reported at the injection site. No major or severe bleedings were observed; all AE associated with bleedings were mild. The most frequently reported bleedings in the volanesorsen group (excluding events at the injection site and laboratory anomalies) were epistaxis in five patients (15%) and petechiae in four patients (12%). These events did not occur in any patient in the placebo group. The only other actual bleeding event reported in more than one patient (n = 2 (6%)) in the volanesorsen group was vaginal bleeding. All bleedings that occurred were classified as mild.

AESI: adverse event of special interest; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients evaluated; n: number of patients with (at least one) event; n.a.: not applicable; (S)AE: (serious) adverse event(s); vs: versus

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ Risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | No deaths occurred |
| Morbidity | ↔ | There is no relevant difference for the benefit assessment. |
| Health-related quality of life | ↔ | There is no relevant difference for the benefit assessment. |
| Side effects | n.a. | not assessable |
| Explanations:<br>↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias<br>↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias<br>↔: no relevant difference<br>∅: no data available<br>n.a.: not assessable | | |

## 2. Number of patients or demarcation of patient groups eligible for treatment

approx. 60 to 120 patients

## 3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Waylivra® (active ingredient: volanesorsen) at the following publicly accessible link (last access: 19 September 2019):

https://www.ema.europa.eu/en/documents/product-information/waylivra-epar-product-information_de.pdf

Treatment with volanesorsen should only be initiated and monitored by physicians who are experienced in the treatment of patients with familial chylomicronemia syndrome (FCS).

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide officially approved training material for medical personnel, including an information package for patients. In particular, the training material contains relevant information on thrombocytopenia and heavy bleeding as well as recommendations on monitoring thrombocytes, including recommendations on dose adjustment before and during treatment.

**4. Treatment costs**

**Annual treatment costs:**

| Designation of the therapy | Annual treatment costs/patient |
|---|---|
| Volanesorsen | € 499,153.63 – 996,394.79 |
| Additionally required SHI services | € 6.78 |
| Total: | € 499,160.41 – 996,401.57 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2020

**II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 20 February 2020.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 20 February 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken