Gemeinsamer Bundesausschuss

Vosoritide (reassessment due to exceeding the € 30 million turnover limit: achondroplasia, ≥ 2 years)

Resolution of: 15 February 2024 Valid until: unlimited
Entry into force on: 15 February 2024
Federal Gazette, BAnz AT 26 03 2024 B5

Therapeutic indication (according to the marketing authorisation of 23 October 2023):

Voxzogo is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

Therapeutic indication of the resolution (resolution of 15 February 2024):

Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

Appropriate comparator therapy:

Best supportive care

"Best supportive care" (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

Extent and probability of the additional benefit of vosoritide compared to the best supportive care:

Indication of non-quantifiable additional benefit

Study results according to endpoints:[1]

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

1 Data from the dossier assessment of the IQWiG (A23-92) and from the addendum (A24-08), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑↑	Advantage in "body height (z score)"
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment overall.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

BMN 111-301 study: RCT, vosoritide + BSC vs placebo + BSC in children and adolescents aged 5 to <18 years over 52 weeks

BMN 111-206 study: RCT, vosoritide + BSC vs placebo + BSC in children aged 2 to < 5 years

Mortality

Endpoint Study	Vosoritide + BSC		Placebo + BSC		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value[b]
Overall mortality (collected as part of AEs)					
206	15	0 (0)	16	0 (0)	-
301	60	0 (0)	61	0 (0)	-

Morbidity

Endpoint; study	Vosoritide + BSC			Placebo + BSC			Intervention vs control
	N[a]	Values at start of study MV (SD)	Change at week 52 LS MV [95% CI]	N[a]	Values at start of study MV (SD)	Change at week 52 LS MV [95% CI]	Mean difference [95% CI] p value
Body height (z score)							
206 Reference population USA[c]	15	−4.27 (0.81)	0.27 [0.04; 0.50]	16	−5.13 (1.15)	−0.06 [−0.28; 0.16]	0.33 [0.00; 0.67]; 0.051
301							
Reference population USA[c]	60	-5.13 (1.11)	0.27 [0.18; 0.36]	61	-5.14 (1.07)	-0.01 [-0.10; 0.09]	0.28 [0.17; 0.39]; < 0.001
Reference population Germany[d] (presented additionally)	60	−5.69 (1.11)	0.28 [0.20, 0.35]	61	−5.68 (1.09)	−0.01 [−0.09, 0.07]	0.28 [0.19, 0.37]; < 0.001
Total							0.28 [0.18; 0.39]; < 0.001
Annualized growth rate [cm/year] (presented additionally)							
206	15	4.74 (1.68)	1.99 [1.31; 2.67]	16	4.20 (1.78)	0.89 [0.23; 1.55]	1.10 [0.13; 2.07]; 0.028
301	60	4.26 (1.53)	1.71 [1.40; 2.01]	61	4.06 (1.20)	0.13 [-0.18; 0.45]	1.57 [1.22; 1.93]; < 0.001
Total							1.51 [1.18; 1.85]; < 0.001
Ratio of upper to lower body segment (presented additionally)							
206	15	2.35 (0.17)	-0.14 [-0.24; -0.04]	16	2.25 (0.19)	-0.08 [-0.18; 0.01]	-0.06 [-0.20; 0.09]; 0.425b
301	60	1.98 (0.20)	-0.03 [-0.06; 0.00]	61	2.01 (0.21)	-0.02 [-0.05; 0.01]	-0.01 [-0.05; 0.02]; 0.506
Total							-0.01 [-0.05; 0.02]; 0.463[e]

Endpoint; study	Vosoritide + BSC			Placebo + BSC			Intervention vs control
	N[a]	Values at start of study MV (SD)	Change at week 52 LS MV [95% CI]	N[a]	Values at start of study MV (SD)	Change at week 52 LS MV [95% CI]	Mean difference [95% CI] p value
Body proportional relationships between the extremities (presented additionally)							
Upper arm length to forearm length							
206	15	1.10 (0.06)	0.00 [-0.07; 0.07]	16	1.08 (0.10)	0.0 [-0.02; 0.11]	-0.05 [-0.15; 0.05]; 0.309
301	58	1.08 (0.14)	0.02 [-0.01; 0.05]	61	1.05 (0.08)	0.03 [0.00; 0.06]	-0.01 [-0.04; 0.02]; 0.568
Total							0.01 [-0.04; 0.02]; 0.364[e]
Ratio of thigh length to length from knee to heel							
206	15	0.64 (0.09)	0.01 [-0.02; 0.04]	16	0.64 (0.07)	-0.01 [-0.04; 0.02]	0.02 [-0.03; 0.06]; 0.490
301	58	0.65 (0.07)	0.01 [0.00; 0.03]	61	0.66 (0.05)	0.02 [0.00; 0.04]	-0.01 [-0.02; 0.01]; 0.568
Total							0.02 [-0.03; 0.06]; 0.490[e]
Ratio of thigh length to shin length							
206	15	1.02 (0.18)	0.01 [-0.05; 0.08]	16	1.05 (0.13)	0.01 [-0.05; 0.07]	0.00 [-0.09; 0.10]; 0.965
301	58	1.07 (0.13)	0.01 [-0.01; 0.04]	61	1.08 (0.11)	0.03 [0.01; 0.06]	-0.02 [-0.05; 0.01]; 0.195
Total							−0.02 [−0.05; 0.01]; 0.213[e]
Ratio of arm span to body height when standing							
206	15	0.87 (0.06)	0.00 [-0.02; 0.02]	16	0.88 (0.03)	0.01 [-0.01; 0.03]	-0.01 [-0.03; 0.02]; 0.620
301	58	0.90 (0.06)	0.00 [-0.01; 0.00]	61	0.90 (0.04)	0.00 [0.00; 0.01]	-0.01 [-0.02; 0.00]; 0.123
Total							-0.01 [-0.02; 0.00]; 0.035[e]

Endpoint; study	Vosoritide + BSC			Placebo + BSC			Intervention vs control
	N[a]	Values at start of study MV (SD)	Change at week 52 LS MV [95% CI]	N[a]	Values at start of study MV (SD)	Change at week 52 LS MV [95% CI]	Mean difference [95% CI] p value
Functional independence (WeeFIM)[f]							
Total score 206	15	63.7 (29.5)	12.3 (18.1)[g]	14	74.8 (20.4)	11.2 (11.1)[g]	1.1 [−10.44; 12.64]; 0.846[b]
Self-care 206	15	22.3 (13.2)	5.8 (7.6)[g]	14	27.1 (10.6)	6.4 (6.0)[g]	-0.6 [−5.84; 4.64]; 0.816[b]
Mobility 206	15	19.0 (8.9)	3.9 (5.8)[g]	14	22.8 (6.4)	2.2 (3.4)[g]	1.7 [−1.96; 5.36]; 0.349[b]
Cognition 206	15	22.5 (10.4)	2.6 (5.8)[g]	14	24.9 (7.2)	2.6 (4.0)[g]	0.0 [−3.82; 3.82]; > 0.999[b]
301	No suitable data						
Coping and beliefs - QoLISSY (parent-reported)[h]							
206	Endpoint not assessed						
Coping 301	28	47.23 (19.93)	-1.26 (13.30)[g]	22	38.70 (19.27)	4.38 (18.74)[g]	-5.64 [-14.75; 3.47]; 0.219[i]
Beliefs 301	30	65.93 (27.80)	-1.46 (23.65)[g]	22	68.48 (27.40)	-4.26 (25.54)[g]	2.80 [-10.99; 16.60]; 0.685[i]
Coping and beliefs- QoLISSY (**patient-reported**, subjects ≥ 8 years)[h]							
206	Endpoint not assessed						
Coping 301	27	50.75 (23.65)	-1.92 (21.54)[g]	36	47.91 (20.49)	-2.26 (23.54)[g]	0.34 [−11.22; 11.90]; 0.953[b]
Beliefs 301	27	58.33 (28.06)	5.79 (26.74)[g]	33	62.31 (26.81)	-2.65 (25.63)[g]	8.44 [−5.13; 22.01]; 0.218[b]

Quality of life

Endpoint; study	Vosoritide + BSC			Placebo + BSC			Intervention vs control
	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SD) [95% CI]	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SD) [95% CI]	Mean difference [95% CI] p value
QoLISSY (parent-reported)[h]							
206	Endpoint not assessed						
Total score 301	31	56.68 (16.61)	-0.90 (16.98)	23	55.70 (20.40)	3.58 (14.47)	-4.47 [-13.29; 4.35]; 0.314[i]
Physical 301	31	47.96 (19.28)	-3.06 (21.28)	23	44.27 (21.97)	3.84 (16.71)	-6.90 [-17.66; 3.85];
Social 301	31	56.86 (20.59)	0.62 (19.27)	23	57.85 (21.08)	6.89 (16.88)	-6.27 [-16.37; 3.83];
Emotional 301	31	65.22 (16.71)	-0.24 (16.68)	23	64.98 (23.31)	0.00 (14.66)	-0.25 [-9.00; 8.51];
Future 301	29	70.78 (25.59)	2.67 (20.22)	22	75.00 (32.51)	0.68 (19.17)	1.99 [-9.25; 13.23];
Effects 301	31	58.27 (21.02)	-4.16 (17.39)	23	59.48 (21.45)	1.09 (16.87)	-5.24 [-14.73; 4.24];
QoLISSY (patient-reported)[h]							
206	Endpoint not assessed						
Total score 301	26	64.59 (17.57)	4.34 (14.42)	35	66.40 (16.05)	-0.88 (19.02)	5.22 [-3.70; 14.14]; 0.246[b]
Physical 301	27	56.36 (20.27)	6.73 (17.50)	37	60.95 (17.51)	-0.13 (21.10)	6.86 [-3.09; 16.81][b]
Social 301	26	66.06 (19.92)	2.44 (15.68)	37	68.02 (20.51)	-2.14 (24.62)	4.58 [-6.38; 15.54][b]
Emotional 301	27	71.36 (21.59)	2.65 (19.77)	35	70.23 (18.15)	0.80 (21.31)	1.85 [-8.73; 12.43][b]

Endpoint; study	Vosoritide + BSC			Placebo + BSC			Intervention vs control
	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SD) [95% CI]	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SD) [95% CI]	Mean difference [95% CI] p value
PedsQL (parent-reported, subjects ≥ 5 to < 8 years)[g]							
206	Endpoint not assessed						
Total score 301	30	71.63 (16.82)	-1.73 (18.00)	21	70.94 (16.76)	0.41 (12.68)	-2.15 [-11.32; 7.03]; 0.640[i]
Physical functioning 301	30	69.96 (23.40)	-3.91 (24.19)	21	69.70 (19.39)	0.00 (17.20)	-3.92 [-16.27; 8.44];
Emotional functioning 301	30	72.83 (17.25)	4.50 (20.48)	21	76.96 (17.24)	0.95 (13.10)	3.55 [-5.91; 13.01];
Social functioning 301	30	68.50 (19.08)	-2.50 (20.88)	21	65.00 (22.91)	4.52 (18.36)	-7.02 [-18.40; 4.35];
School functioning 301	30	76.17 (16.49)	-3.67 (18.75)	21	72.83 (21.99)	-3.57 (15.98)	-0.10 [-10.20; 10.01];
PedsQL (patient-reported, subjects ≥ 8 years)[g]							
206	Endpoint not assessed						
Total score 301	25	74.07 (11.87)	0.85 (13.80)	33	75.32 (14.98)	-2.62 (15.06)	3.47 [−4.25; 11.19]; 0.372[b]
Physical functioning 301	25	77.37 (14.11)	-0.24 (14.04)	33	77.03 (17.72)	-2.02 (16.27)	1.78 [-6.38; 9.94][b]
Emotional functioning 301	24	75.18 (16.47)	1.88 (17.68)	33	76.29 (18.36)	0.11 (19.50)	1.77 [-8.32; 11.86][b]
Social functioning 301	25	73.39 (19.72)	-0.20 (25.68)	33	71.14 (19.52)	-5.61 (23.48)	5.41 [-7.58; 18.40][b]
School functioning 301	25	68.39 (18.56)	2.40 (17.80)	33	75.93 (16.93)	-3.41 (18.97)	5.81 [−4.00; 15.62][b]

Endpoint; study	Vosoritide + BSC			Placebo + BSC			Intervention vs control
	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SD) [95% CI]	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SD) [95% CI]	Mean difference [95% CI] p value
ITQOL (children ≥ 2 to < 5 years)							
General health 301	12	82.67 (17.71)	5.42 (16.85)	12	82.14 (15.90)	3.75 (17.60)	1.67 [-12.92; 16.25]; 0.815[i]
Physical abilities 206	14	68.44 (31.25)	7.38 (23.94)	14	77.90 (21.07)	-6.01 (9.83)	13.39 [-1.19; 27.96]; 0.070[i]
Growth and development 206	14	77.00 (17.22)	3.66 (9.05)	14	76.17 (13.95)	4.82 (11.62)	-1.16 [-9.25; 6.93]; 0.770[i]
Pain 206	14	87.78 (14.39)	-1.19 (20.11)	14	82.22 (12.94)	-1.19 (20.37)	0.00 [-15.73; 15.73]; > 0.999[i]
Temperament and mood 206	14	82.41 (9.27)	0.86 (4.76)	14	82.87 (8.49)	4.79 (9.60)	-3.93 [-9.92; 2.07]; 0.186[i]
Behaviour 206	14	83.75 (11.60)	0.00 (9.81)	13	78.75 (15.79)	2.73 (23.36)	-2.73 [-17.55; 12.10]; 0.702[i]
Overall behaviour 206	14	87.00 (15.56)	2.14 (19.29)	13	86.67 (19.24)	1.15 (21.42)	0.99 [-15.15; 17.12]; 0.901[i]
Getting along with others 206	No suitable data						
General health perception 206	14	66.11 (13.57)	3.05 (12.44)	13	65.11 (21.00)	-1.07 (15.43)	4.12 [-6.96; 15.19]; 0.451[i]
Change in health 206	13	3.86 (0.66)	0.15 (0.69)	13	3.50 (0.85)	0.08 (0.64)	0.08 [-0.46; 0.62]; 0.771[i]
301	Endpoint not assessed						

Side effects

Endpoint Study	Vosoritide + BSC		Placebo + BSC		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p value[b]
Total adverse events – presented additionally					
206	15	15 (100.0)	16	16 (100.0)	-
301	60	59 (98.3)	61	60 (98.4)	-
Serious adverse events (SAE)[j]					
206	15	1 (6.7)	16	1 (6.3)	1.07 [0.07; 15.57]; > 0.999
301	60	3 (5.0)	61	4 (6.6)	0.76 [0.18; 3.26]; 0.802
Total					0.82 [0.23; 2.94]; 0.763[e]
Severe adverse events (CTCAE grade ≥ 3)[j]					
206	15	0 (0)	16	0 (0)	–
301	60	3 (5.0)	61	3 (4.9)	1.02 [0.21; 4.84]; > 0.999
Therapy discontinuation due to adverse events					
206	15	0 (0)	16	0 (0)	–
301	60	1 (1.7)	61	0 (0)	3.05 [0.13; 73.40]; 0.367
Reactions at the injection site (AEs)					
206	15	12 (80.0)	16	7 (43.8)	1.83 [0.99; 3.37]; 0.042
301	60	51 (85.0)	61	50 (82.0)	1.04 [0.88; 1.22]; 0.710
Total					1.13 [0.96; 1.33]; 0.135[e]

a. Number of patients who were taken into account in the evaluation for calculating the effect estimate (for the study 206, this corresponds to the relevant sub-population); the values at start of study can be based on other patient numbers.
b. IQWiG calculations

c. Evaluation based on the US reference population of the CDC with average stature.
d. Post-hoc evaluation based on the growth data from Germany on average height published by the Robert Koch Institute
e. IQWiG calculation: Meta-analysis with fixed effect
f. Higher (increasing) values mean a better functional independence; positive effects (intervention minus control) mean an advantage for the intervention (total score scale range 18 to 126)
g. MV (SD)
h. Higher (increasing) values mean a lower morbidity / better health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).
i. No data available on the calculation of the p value; presumably t-test
j. Contain potentially disease-related events; in the present data basis, it is assumed that this does not have a relevant influence on the results for SAEs and severe AEs

Abbreviations used:
BSC: best supportive care; CDC: Centers for Disease Control and Prevention (USA); CTCAE: Common Terminology Criteria for Adverse Events; n.d.: no data available; CI: confidence interval; LS: Least Squares; MD: mean difference; MV: mean value; n: number of patients with (at least 1) event; N: Number of patients evaluated; PedsQL: Paediatric Quality of Life Inventory; QoLISSY: The Quality of Life of Short Stature Youth; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SAE: serious adverse event; AE: adverse event; WeeFIM: Paediatric Functional Independence Measure II

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

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

Approx. 330 to 460 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 Voxzogo (active ingredient: vosoritide) at the following publicly accessible link (last access: 10 January 2024):
https://www.ema.europa.eu/en/documents/product-information/voxzogo-epar-product-information_en.pdf

Treatment with vosoritide must only be initiated and monitored by doctors experienced in the treatment of patients with growth disorders or skeletal dysplasias.

4. Treatment costs

Annual treatment costs:

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Vosoritide	€ 225,680.60
Best supportive care	Different from patient to patient

Designation of the therapy	Annual treatment costs/ patient
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 January 2024

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.