Gemeinsamer Bundesausschuss

Vosoritide (new therapeutic indication: achondroplasia, ≥ 4 months to < 2 years)

Resolution of: 16 May 2024 valid until: unlimited
Entry into force on: 16 May 2024
Federal Gazette, BAnz AT 09 07 2024 B1

New therapeutic indication (according to the marketing authorisation of 25 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 16 May 2024):

Voxzogo is indicated for the treatment of achondroplasia in patients 4 months to < 2 years of age whose epiphyses are not closed.

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

Patients 4 months to < 2 years of age 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:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Patients 4 months to < 2 years of age with achondroplasia and whose epiphyses are not closed

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-116) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	In the 206 study (cohorts 2 and 3), no relevant differences for the benefit assessment, even taking into account the results of children ≥ 2 years of age.
Morbidity	↑	In the 206 study (cohorts 2 and 3), no relevant differences for the benefit assessment. In addition, advantage in the endpoint "body height (z-score)" taking into account the results of children ≥ 2 years of age.
Health-related quality of life	↔	No assessable data are available in the 206 study (cohorts 2 and 3). Furthermore, no relevant differences for the benefit assessment considering the results of children ≥ 2 years of age.
Side effects	↔	In the 206 study (cohorts 2 and 3), no relevant differences for the benefit assessment. In detail, disadvantage in specific AE reactions at the injection site. In addition, no relevant differences taking into account the results of children ≥ 2 years of age.
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 111-206 study: RCT, vosoritide + BSC vs placebo + BSC, children aged 0 to < 5 years of age (cohort 1: ≥ 24 to < 60 months, cohort 2: ≥ 6 to < 24 months, cohort 3: 0 to < 6 months).

Relevant sub-populations: Children from 4 months to < 2 years of age, corresponding to cohort 2 and cohort 3 (approx. 51.6% of the study population).

Mortality

Endpoint	**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)*					
Cohort 2	8	0 (0)	8	0 (0)	–
Cohort 3	9	1 (11.1)	8	0 (0)	2.70 [0.13; 58.24]; 0.522

Morbidity

Endpoint	**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]	MD [95% CI]; p value
Body height (z score)							
Cohort 2	8	-3.39 (0.84)	0.02 [−0.38; 0.41]	8	-4.21 (1.24)	-0.19 [−0.58; 0.20]	0.21 [-0.37; 0.79]; 0.443[c]
Cohort 3	9	-3.34 (0.34)	-0.68 [-1.21; -0.15][d]	8	-2.65 (0.28)	-0.91 [-1.36; -0.45][d]	0.23 [-0.45, 0.91]; 0.508[c,d]
Total							0.22 [−0.22; 0.66]; 0.332[e]

Endpoint	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]	MD [95% CI]; p value
Annualized growth rate [cm/year] *(presented additionally)*							
Cohort 2	*8*	*11.51 (4.66)*	*-2.36 [−3.22; -1.50]*	*8*	*10.55 (4.78)*	*-3.00 [−3.86; -2.13]*	*0.63 [−0.60; 1.87) 0.280[f]*
Cohort 3	*9*	*21.19 (0.93)*	*-9.34 [-10.78; -7.91][d]*	*8*	*19.45 (2.67)*	*-10.14 [-11.48; -8.79][d]*	*0.79 [−1.08; 2.67]; 0.407[d,f]*
Total							*0.68 [−0.35; 1.71]; 0.197[e]*
Ratio of upper to lower body segment *(presented additionally)*							
Cohort 2	No suitable data[g]						
Cohort 3	No suitable data[g]						
Body proportional relationships between the extremities[h] *(presented additionally)*							
Cohort 2	No suitable data[g]						
Cohort 3	No suitable data[g]						
Functional independence (WeeFIM)[i]							
Total score							
Cohort 2	7	32.3 (13.1)	14.7 (18.9) [j]	6	28.3 (13.5)	16.2 (14.6) [j]	−1.50 [−22.41; 19.41]; 0.877[k]
Cohort 3	No suitable data[l]						
Self-care							
Cohort 2	7	10.1 (2.0)	3.0 (3.6) [j]	6	9.8 (2.4)	3.7 (2.3) [j]	−0.70 [−4.47; 3.07]; 0.691[k]
Cohort 3	No suitable data[l]						
Mobility							

Endpoint	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]	MD [95% CI]; p value
Cohort 2	7	9.4 (5.4)	7.6 (7.8) [j]	6	9.4 (4.9)	7.0 (7.5)[j]	0.60 [−8.79; 9.99]; 0.891[k]
Cohort 3	No suitable data[l]						
Cognition							
Cohort 2	7	12.7 (7.7)	4.1 (9.4)[j]	6	9.1 (6.4)	5.5 (7.6)[j]	−1.40 [−11.97; 9.17]; 0.776[k]
Cohort 3	No suitable data[l]						

Health-related quality of life

Endpoint	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]	MD [95% CI]; p value
ITQoL							
Cohort 2	No suitable data[g]						
Cohort 3	No suitable data[g]						

Side effects

Endpoint	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]
***AEs** (presented additionally)*[m]					
Cohort 2	*8*	*8 (100.0)*	*8*	*8 (100.0)*	–
Cohort 3	*9*	*9 (100.0)*	*8*	*8 (100.0)*	–

Endpoint	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]
SAEs[m]					
Cohort 2	8	0 (0)	8	2 (25.0)	0.20 [0.01; 3.61]; 0.212
Cohort 3	9	2 (22.2)	8	3 (37.5)	0.59 [0.13; 2.70]; 0.629
Total					0.42 [0.11; 1.60]; 0.203[n]
Severe AEs[m,o]					
Cohort 2	8	0 (0)	8	0 (0)	–
Cohort 3	9	2 (22.2)	8	3 (37.5)	0.59 [0.13; 2.70]; 0.629
Discontinuation due to AEs					
Cohort 2	8	0 (0)	8	0 (0)	–
Cohort 3	9	0 (0)	8	0 (0)	–
Reactions at the injection site (HLT, AEs)[p]					
Cohort 2	8	8 (100.0)	8	4 (50.0)	1.89 [0.96; 3.70]; 0.028
Cohort 3	9	9 (100.0)	8	6 (75.0)	1.32 [0.86; 2.02]; 0.145
Total					1.54 [1.06; 2.26]; 0.025[n]

a. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
b. IQWiG calculation of RR, CI (asymptotic) and p value (unconditional exact test, CSZ-method). In the case of 0 events in one study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI. Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods.
c. LS mean values and difference of LS mean values from ANCOVA with the covariates treatment, sex, age stratum, baseline age, baseline AGV and baseline z-score body height
d. According to the information provided by the pharmaceutical company, based on 10 imputed data sets, but it is unclear what the pharmaceutical company means by data sets. The sensitivity analyses presented in Module 4 A show replacement of missing values for a patient.
e. IQWiG calculation: Fixed-effect meta-analysis (inverse variance method)
f. LS mean values and difference of LS mean values from ANCOVA with the covariates treatment, sex, age stratum, baseline age and baseline AGV
g. No suitable data available.
h. Upper arm length to forearm length, thigh length to knee-to-heel length, thigh length to shin length and arm span to body height
i. 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).
j. MV (SD)
k. Effect, CI and p value: IQWiG calculation (t-test)
l. The WeeFIM was not collected in patients < 6 months of age, so no suitable data are available for cohort 3 (0 to < 6 months) due to missing values at baseline.

m. 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.
n. IQWiG calculation: Meta-analysis with fixed effect (Mantel and Haenszel method)
o. Operationalised as CTCAE grade ≥ 3.
p. The most common PTs in both cohorts were erythema at the injection site and reaction at the injection site.

Abbreviations used:
AGV: annualized growth velocity; ANCOVA: covariance analysis; BSC: best supportive care; CTCAE: common terminology criteria for adverse events; HLT: high-level term; ITQoL: infant and toddler quality of life questionnaire; CI: confidence interval; LS: least squares; MD: mean difference; MV: mean value; N: number of patients evaluated; n: number of patients with (at least one) event:; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SAE: serious adverse event; AE: adverse event; vs: versus; WeeFIM: paediatric functional independence measure II; WHO: World Health Organisation; vs: versus

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

Patients 4 months to < 2 years of age with achondroplasia and whose epiphyses are not closed

approx. 35 – 49 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: 2 April 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 4 months to < 2 years of age 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
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 May 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 4 months to < 2 years of age 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.