Vosoritide (achondroplasia)

Addendum to Project A23-92 (dossier assessment)[1]

ADDENDUM

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Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	Best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITQOL	Infant Toddler Quality of Life Questionnaire-97
PedsQL	Pediatric Quality of Life Inventory
QoLISSY	Quality of Life of Short Stature Youth
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 9 January 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-92 (Vosoritide – Benefit assessment according to §35a Social Code Book V) [1].

In its comments, the pharmaceutical company (hereinafter referred to as the "company") submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit. The commission comprises the assessment of the Infant Toddler Quality of Life Questionnaire-97 (ITQOL), taking into account the information provided in the dossier [2] and the documents subsequently submitted in the commenting procedure [3]. In addition, the commission comprises the assessment of the analyses of the parent-reported versions of the instruments Pediatric Quality of Life Inventory (PedsQL) and Quality of Life of Short Stature Youth (QoLISSY) for the age group of ≥ 5 to < 8 years of the BMN 111-301 study, which was already presented with the dossier and incorrectly described as missing in benefit assessment A23-92. The subsequent assessment thus corrects the error in benefit assessment A23-92.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Benefit assessment A23-92 used the randomized controlled trials (RCTs) BMN 111-206 and BMN 111-301 to assess the added benefit of vosoritide in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with achondroplasia 2 years of age and older whose epiphyses are not closed [1].

PedsQL or QoLISSY (age group ≥ 5 to < 8 years)

In its dossier, the company presented patient-reported and parent-reported versions of the PedsQL and QoLISSY instruments for the BMN 111-301 study (patients aged ≥ 5 to < 18 years) to record health-related quality of life and the morbidity outcome of coping and beliefs. In benefit assessment A23-92, the directly patient-reported versions of the instruments were preferably used to assess an added benefit. However, the patient-reported versions were only recorded in patients aged ≥ 8 to < 18 years, while the parent-reported versions were already recorded in patients from the age of ≥ 5 years. Since the age group of ≥ 8 to < 18 years is adequately represented by the patient-reported versions of PedsQL and QoLISSY, the parent-reported versions were only considered for the age group of ≥ 5 to < 8 years in benefit assessment A23-92. In the commenting procedure, the company pointed out that (contrary to the description in A23-92) separate analyses for the PedsQL and QoLISSY instruments for the age group of ≥ 5 to < 8 years were already available in the dossier (Appendix Module 4 A) at the time of the benefit assessment [2]. As part of an error correction, the analyses of the parent-reported versions of the PedsQL and QoLISSY for the age group of ≥ 5 to < 8 years in the BMN 111-301 study are used below for the benefit assessment.

ITQOL (≥ 2 to < 5 years)

The company used the ITQOL instrument to analyse health-related quality of life in patients in the BMN 111-206 study (patients aged 0 to < 5 years). For the patients in the relevant subpopulation of benefit assessment A23-92, it presented separate analyses of the ITQOL for the age group of ≥ 2 to < 5 years in its dossier. Based on the information available, it was not possible to evaluate the validity of the ITQOL at the time of the benefit assessment. The ITQOL was therefore not used for assessing the added benefit of vosoritide in the present therapeutic indication. With its comments, the company submitted the version of the ITQOL used in the study. The ITQOL is assessed below.

Available analyses

The company presented only continuous analyses for the PedsQL, the QoLISSY and the ITQOL. In principle, however, responder analyses are also possible for these outcomes, which, conducted post hoc, should correspond to the response criterion of exactly 15% of the scale range of the instrument used.

2.1 Parent-reported analyses of the PedsQL for the age group of ≥ 5 to < 8 years on health-related quality of life

In benefit assessment A23-92, health-related quality of life was already evaluated for patients ≥ 8 years of age using the self-reported version of the PedsQL. Based on the information available in the dossier, the health-related quality of life in patients aged ≥ 5 to < 8 years is evaluated below using the parent-reported version of the PedsQL.

Risk of bias and certainty of conclusions

The risk of bias for the outcome of health-related quality of life, recorded using PedsQL, is rated as high overall. This is due to large differences between the treatment arms (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis. Due to the high risk of bias, at most a hint, e.g. of an added benefit, can be determined for the outcome of health-related quality of life, recorded using PedsQL.

Results

Table 1 summarizes the results for the parent-reported version of the PedsQL for patients aged ≥ 5 to < 8 years.

Table 1: Results (health-related quality of life, ≥ 5 to < 8 years) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study Outcome category	Vosoritide + BSC			Placebo + BSC			Vosoritide + BSC vs. placebo + BSC
Outcome	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	MD [95% CI]; p-value[b]
BMN 111-301							
Health-related quality of life							
PedsQL (parent-reported)[c, d]							
Total score	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
Physical functioning	30	69.96 (23.40)	−3.91 (24.19)	21	69.70 (19.39)	0.00 (17.20)	−3.92 [−16.27; 8.44]; 0.527
Emotional functioning	30	72.83 (17.25)	4.50 (20.48)	21	76.96 (17.24)	0.95 (13.10)	3.55 [−5.91; 13.01]; 0.455
Social functioning	30	68.50 (19.08)	−2.50 (20.88)	21	65.00 (22.91)	4.52 (18.36)	−7.02 [−18.40; 4.35]; 0.220
School functioning	30	76.17 (16.49)	−3.67 (18.75)	21	72.83 (21.99)	−3.57 (15.98)	−0.10 [−10.20; 10.01]; 0.985

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. No information on the calculation of the p-value, based on a comparison of calculations conducted by the Institute with the calculations of the company in the context of dossier assessment A23-92, presumably t-test.
c. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
d. Includes patients aged ≥ 5 to < 8 years.

BSC: best supportive care; CI: confidence interval; MD: mean difference; N: number of analysed patients; PedsQL: Pediatric Quality of Life Inventory; RCT: randomized controlled trial; SD: standard deviation

For the outcome of health-related quality of life, recorded using the parent-reported version of the PedsQL, no significant difference between treatment groups was shown in children aged ≥ 5 to < 8 years, neither in the total score nor in the individual functions. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Subgroups and other effect modifiers

When applying the methods described in A23-92, the available subgroup results show no relevant effect modifications.

2.2 Parent-reported analyses of the QoLISSY for the age group of ≥ 5 to < 8 years on morbidity and health-related quality of life

In benefit assessment A23-92, health-related quality of life as well as the morbidity outcome of coping and beliefs was evaluated for patients ≥ 8 years of age based on the self-reported version of the QoLISSY. Based on the information available in the dossier, health-related quality of life as well as the outcome of coping and beliefs in patients aged ≥ 5 to < 8 years is evaluated below using the parent-reported version of the QoLISSY.

Risk of bias and certainty of conclusions

The risk of bias for the morbidity outcome of coping and beliefs as well as health-related quality of life, each recorded using QoLISSY, is rated as low overall. For these outcomes, at most indications, e.g. of an added benefit, can therefore be determined.

Results

Table 2 shows the results of the morbidity outcome of coping and beliefs as well as the results of health-related quality of life in patients aged ≥ 5 to < 8 years, which were recorded using the parent-reported version of the QoLISSY.

Table 2: Results (morbidity and health-related quality of life, ≥ 5 to < 8 years) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study outcome category / Outcome	Vosoritide + BSC			Placebo + BSC			Vosoritide + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	MD [95% CI]; p-value[b]
BMN 111-301							
Morbidity							
Coping and beliefs (QoLISSY [parent-reported])[c, d]							
Coping	28	47.23 (19.93)	−1.26 (13.30)	22	38.70 (19.27)	4.38 (18.74)	−5.64 [−14.75; 3.47]; 0.219
Beliefs	30	65.93 (27.80)	−1.46 (23.65)	22	68.48 (27.40)	−4.26 (25.54)	2.80 [−10.99; 16.60]; 0.685
Health-related quality of life							
QoLISSY (parent-reported)[c, d]							
Total score	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
Physical	31	47.96 (19.28)	−3.06 (21.28)	23	44.27 (21.97)	3.84 (16.71)	−6.90 [−17.66; 3.85]; 0.203
Social	31	56.86 (20.59)	0.62 (19.27)	23	57.85 (21.08)	6.89 (16.88)	−6.27 [−16.37; 3.83]; 0.219
Emotional	31	65.22 (16.71)	−0.24 (16.68)	23	64.98 (23.31)	0.00 (14.66)	−0.25 [−9.00; 8.51]; 0.955
Future	29	70.78 (25.59)	2.67 (20.22)	22	75.00 (32.51)	0.68 (19.17)	1.99 [−9.25; 13.23]; 0.723
Effects	31	58.27 (21.02)	−4.16 (17.39)	23	59.48 (21.45)	1.09 (16.87)	−5.24 [−14.73; 4.24]; 0.272

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. No information on the calculation of the p-value, based on a comparison of calculations conducted by the Institute with the calculations of the company in the context of dossier assessment A23-92, presumably t-test.
c. Higher (increasing) values indicate lower morbidity/better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
d. Includes patients aged ≥ 5 to < 8 years.

BSC: best supportive care; CI: confidence interval; MD: mean difference; N: number of analysed patients; QoLISSY: Quality of Life of Short Stature Youth; RCT: randomized controlled trial; SD: standard deviation

No significant difference between treatment groups was shown for patients aged ≥ 5 to < 8 years for the morbidity outcome of coping and beliefs or for health-related quality of life, each recorded using the parent-reported version of the QoLISSY. In each case, there is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Subgroups and other effect modifiers

When applying the methods described in A23-92, the available subgroup results show no relevant effect modifications.

2.3 Analyses of the ITQOL on health-related quality of life

In its comments, the company provided further information on the ITQOL. The ITQOL is a parent-reported instrument for use in infants and toddlers from 2 months to 5 years of age. It was recorded only in Study BMN 111-206, using the full version with 97 items. The items are summarized in a total of 13 subscales, of which 10 subscales cover the child's general health, and 3 subscales cover the effect on the child's parents and family. The reference period for the items is the past 4 weeks. In contrast, items that record a global change use a reference period of 1 year. Accordingly, these items are not used for patients < 12 months of age. The items are answered on a 4 to 5-point Likert scale. The results of the subscales are transformed onto a scale from 0 to 100, with higher scores indicating better health status [4]. In the BMN 111-206 study, the ITQOL was recorded at baseline, Week 26, Week 52 and at premature study discontinuation.

In the present research question, the analyses of health-related quality of life, recorded using ITQOL, are used to assess the added benefit of vosoritide + BSC in comparison with BSC. However, with the 3 subscales "parental impact – emotional", "parental impact – time", and "family cohesion", the ITQOL also records the effects of treatment with vosoritide on the patient's parents and family environment. Such effects are not directly patient relevant and are therefore not used to assess the added benefit.

Risk of bias and certainty of conclusions

The risk of bias for the outcome of health-related quality of life, recorded using ITQOL, is rated as high overall. This is due to the high proportion (> 10%) of patients who were not considered in the analysis, and large differences between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis. Due to the large difference between the treatment groups (> 15 percentage points) with regard to the proportion of patients who were not considered in the analysis, no suitable data is available for the subscale "getting along with others". Due to the high risk of bias, at most hints, e.g. of an added benefit, can be determined for the outcome of health-related quality of life, recorded using ITQOL.

Results

Table 3 summarizes the results for the outcome of health-related quality of life, recorded using ITQOL, for patients aged ≥ 2 to < 5 years.

Table 3: Results (health-related quality of life, ≥ 2 to < 5 years) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study outcome category / Outcome	Vosoritide + BSC			Placebo + BSC			Vosoritide + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	MD [95% CI]; p-value[b]
BMN 111-206							
Health-related quality of life							
ITQOL[c, d]							
Overall health	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
Physical abilities	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
Growth and development	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
Pain	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
Temperament and moods	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
Behaviour	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
General behaviour	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
Getting along with others	No suitable data[e]						
General health perception	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
Change in health[f]	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

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. No information on the calculation of the p-value, based on a comparison of calculations conducted by the Institute with the calculations of the company in the context of dossier assessment A23-92, presumably t-test.
c. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
d. Includes patients aged ≥ 24 to < 60 months.
e. Large difference between the treatment groups (> 15 percentage points) regarding the patients who were not considered in the analysis. Irrespective of this, there is no statistically significant effect in this subscale either.
f. There are uncertainties as to whether there was an appropriate transformation of the results for this subscale of the ITQOL.

BSC: best supportive care; CI: confidence interval; ITQOL: Infant Toddler Quality of Life Questionnaire; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation

The mean and extreme values cited by the company (minimum: 3; maximum 5), on a scale of 0 to 100, appear very low for the subscale “change in health”. There are uncertainties as to whether there was an appropriate transformation of the results for this subscale of the ITQOL.

Due to large differences between the treatment arms (> 15 percentage points) with regard to the patients who were not considered in the analysis, there are no suitable data for the subscale “getting along with others” for assessing the added benefit. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

For the outcome of health-related quality of life as measured using ITQOL, no significant differences between treatment groups were found for any of the other subscales. In each case, there is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Subgroups and other effect modifiers

Table 4 summarizes the subgroup results of the comparison of vosoritide + BSC versus BSC for the outcome of health-related quality of life, recorded using ITQOL, in patients aged ≥ 2 to < 5 years.

Table 4: Subgroups (health-related quality of life, ≥ 2 to < 5 years) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study Outcome	Vosoritide + BSC			Placebo + BSC			Vosoritide + BSC vs. placebo + BSC
Characteristic Subgroup	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SD)	MD [95% CI]; p-value[b]
BMN 111-206							
Temperament and moods (ITQOL)[c]							
Sex							
Male	6	81.5 (10.2)	1.1 (4.7)	7	77.0 (7.5)	10.9 (6.1)	−9.84 [−16.56; −3.12]; 0.008 SMD −1.67 [−2.93; −0.35]
Female	8	83.2 (9.0)	0.7 (5.1)	7	88.0 (5.6)	−1.3 (8.7)	2.04 [−5.79; 9.86]; 0.854
Total						Interaction:	p-value = 0.021[d]
Age at baseline [months]							
24 to < 36	8	81.9 (7.9)	−1.7 (4.3)	3	73.6 (9.1)	11.6 (4.9)	−13.31 [−20.12; −6.51]; 0.002 SMD −2.74 [−4.52; −0.88]
36 to < 60	6	82.9 (11.3)	4.3 (2.8)	11	85.2 (6.9)	2.9 (9.9)	1.38 [−5.53; 8.29]; 0.672
Total						Interaction:	p-value = 0.021[d]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. No information on the calculation of the p-value, based on a comparison of calculations conducted by the Institute with the calculations of the company in the context of dossier assessment A23-92, presumably t-test.
c. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
d. p-value from analysis of variance with corresponding interaction term.

BSC: best supportive care; CI: confidence interval; ITQOL: Infant Toddler Quality of Life Questionnaire; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference

For the temperament and moods subscale of the ITQOL, there were effect modifications by the characteristic of sex and the characteristic of age at baseline.

The effect modifications cannot be assessed without examining for cross-interactions. Due to the described limitation, the subgroup results of these characteristics are not used for the benefit assessment; the benefit assessment is based on the results of the total population.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of vosoritide from dossier assessment A23-92.

The following Table 5 shows the result of the benefit assessment of vosoritide taking into account both dossier assessment A23-92 and the present addendum.

Table 5: Vosoritide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with achondroplasia[b] 2 years of age and older whose epiphyses are not closed	BSC[c]	Indication of non-quantifiable added benefit[d]

a. Presented is the respective ACT specified by the G-BA.
b. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
d. No data are available for patients aged ≥ 15 years at the start of treatment.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vosoritid (Achondroplasie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 12.01.2024]. URL: https://dx.doi.org/10.60584/A23-92.

2. BioMarin International. Vosoritid (Achondroplasie); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 11.01.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/992/#dossier.

3. BioMarin International. Stellungnahme zum IQWiG-Bericht Nr. 1682: Vosoritid (Achondroplasie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/992/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. HealthActCHQ. ITQOL: Infant Toddler Quality of Life Questionnaire [online]. 2021. URL: https://www.healthactchq.com/survey/itqol.