Vosoritide
(achondroplasia, ≥ 4 months to < 2 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A23-116 Version: 1.0 Status: 27 Feb 2024 DOI: 10.60584/A23-116_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Vosoritid (Achondroplasie,* ≥ 4 Monate bis < 2 Jahre*) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Vosoritide (achondroplasia, ≥ 4 months to < 2 years) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

28 November 2023

Internal Project No.

A23-116

DOI-URL

https://doi.org/10.60584/A23-116_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Johannes Wagner, Lübben, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Florian Innig.

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Lukas Gockel
- Merlin Bittlinger
- Dorothee Ehlert
- Lisa Junge
- Ulrike Lampert
- Mattea Patt
- Daniela Preukschat
- Pamela Wronski

Keywords

Vosoritide, Achondroplasia, Infant, Child, Adolescent, Benefit Assessment, NCT03583697, NCT03989947

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of figures

Page

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CDC	Centers for Disease Control and Prevention
CTCAE	Common Terminology Criteria for Adverse Events
EPAR	The European Public Assessment Report
FGFR3	fibroblast growth factor receptor 3
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 and Toddler Quality of Life Questionnaire
NFAH	near-final adult height
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
WeeFIM	Pediatric Functional Independence Measure II

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug vosoritide. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 28 November 2023.

Research question

The aim of the present report was to assess the added benefit of vosoritide in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients aged 4 months to < 2 years with achondroplasia.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of vosoritide

Therapeutic indication	**ACT**[a]
Patients aged 4 months to < 2 years with achondroplasia[b]	BSC[c]
a. Presented is the 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. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee	

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 52 weeks were used for deriving any added benefit.

Study pool and study design

The study pool for the benefit assessment comprises the study BMN 111-206 (hereinafter referred to as "Study 206"). To assess the effects of longer-term treatment with vosoritide, partial results of the long-term data presented by the company were considered as supportive information. In addition to the aforementioned study, these contain data from the BMN 111-208 study.

Study 206

Study 206 is a phase 2, double-blind, 52-week RCT assessing vosoritide versus placebo in children aged 0 to < 5 years with genetically confirmed achondroplasia.

Patients included in Cohorts 1 (≥ 2 to < 5 years) and 2 (≥ 6 months to < 2 years) had to have completed a prior observation phase of at least 6 months in the BMN 111-901 study. In addition, this observation phase had to include a recording of body height or body length, which took place ≥ 6 months before screening of Study 206. Patients in Cohort 3 (0 to < 6 months) had to have completed an observation phase of at least 3 months, either by participating in the BMN 111-901 study or as part of Study 206 (for children aged 0 to ≤ 3 months).

In Study 206, a total of 32 patients were randomized to the intervention arm and 32 patients to the comparator arm.

Study 206 included patients aged 0 to < 5 years. However, the present research question only comprises patients aged 4 months to < 2 years with genetically confirmed achondroplasia. Therefore, only the analyses for the relevant age group were used for the benefit assessment. This comprises Cohort 2 (aged ≥ 6 to < 24 months, 8 patients each in the intervention and the comparator arm) and Cohort 3 (aged 0 to < 6 months, 9 patients in the intervention arm and 8 in the comparator arm) of Study 206. Due to the observation phase required in advance (see above), patients included in Cohort 3 received the first dose of vosoritide at an age of 4 months at the earliest. Cohort 1 is therefore no longer considered below. Where possible and appropriate, Cohorts 2 and 3 were summarized in a meta-analysis. Patients in Cohorts 2 and 3 generally received approval-compliant treatment with subcutaneous vosoritide 30 µg/kg once daily or with subcutaneous placebo once daily. In addition to the study medication, concomitant treatments were permitted at the discretion of the investigator. Overall, adequate implementation of the ACT BSC in Study 206 is assumed.

The primary outcome of Study 206 was the change in body length/height z-score as well as safety and tolerability. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, and health-related quality of life.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for Study 206. The results for the outcome of functional independence, recorded using the Pediatric Functional Independence Measure II (WeeFIM), have a high risk of bias for Cohort 2 (suitable data for this outcome are lacking for Cohort 3). The risk of bias of all other outcomes for which suitable data are available is rated as low.

Because of this, no more than a hint, e.g. of an added benefit, can be determined for the outcome of functional independence (WeeFIM). At most indications, e.g. of an added benefit, can be determined for all other outcomes for which suitable data are available.

Results

Mortality

Overall survival

No deaths occurred in Cohort 2 of Study 206. There was no significant difference between treatment groups in Cohort 3. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Height (z-score)

For the outcome of height (z-score), the meta-analysis of Cohorts 2 and 3 of Study 206 did not show any significant differences between treatment groups. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Due to the limited time period and the limited number of patients, the analyses of the long-term data on the outcome of height (z-score) presented by the company are currently not sufficient to assess the long-term effect of vosoritide at an early start of treatment (younger than 2 years).

Upper to lower body segment ratio and body proportion ratios of the extremities

No suitable data are available for the outcomes of upper to lower body segment ratio and body proportion ratios of the extremities. 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.

Functional independence (WeeFIM)

In Study 206, the WeeFIM was only recorded from the age of 6 months. For Cohort 3 (0 to < 6 months), therefore, no suitable data are available to assess the functional independence. For Cohort 2 (≥ 6 months to < 2 years), there was no significant difference between the treatment groups for the outcome of functional independence, recorded using WeeFIM. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

ITQOL

There are no suitable data for health-related quality of life, recorded with the Infant and Toddler Quality of Life Questionnaire (ITQOL). There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, the meta-analysis of Cohorts 2 and 3 of Study 206 did not show any significant differences between treatment groups. There is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Severe AEs

In Cohort 2 of Study 206, there were no events in the outcome of severe AEs. There was no significant difference between treatment groups in Cohort 3. In each case, there is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", there were no events in either Cohort 2 or Cohort 3 of Study 206. There is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Injection site reactions (AE)

For the outcome of injection site reactions (AE), the meta-analysis of Cohorts 2 and 3 of Study 206 showed a significant difference between treatment groups to the disadvantage of vosoritide. This difference was no more than marginal, however. There is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug vosoritide in comparison with the ACT is assessed as follows:

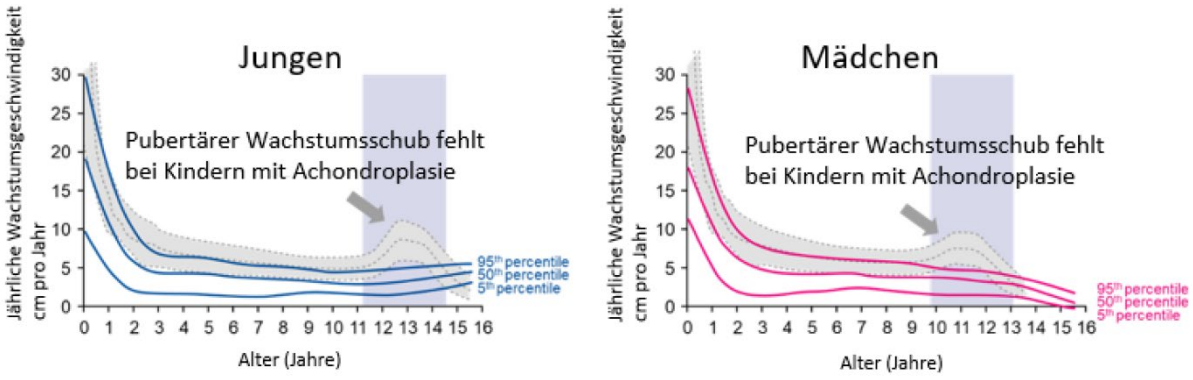
For patients aged 4 months to < 2 years with achondroplasia, the results of Study 206 did not provide any hint of lesser benefit or added benefit of vosoritide compared with the ACT BSC. Overall, the evidence available from Study 206 and Study BMN 111-208 for the age group ≥ 4

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

months to < 2 years only comprises a few patients (vosoritide 17 vs. placebo 16) and is therefore limited.

In particular, the long-term data from the BMN 111-208 study are currently not sufficient to assess the long-term effect of vosoritide at an early start of treatment (younger than 2 years). Currently, there are only limited data available covering a period of 3.5 years (maximum meaningful period: Cohort 2 = 3.5 years; Cohort 3 = 2 years) for up to 23 patients, which do not allow any clear conclusions to be drawn.

Benefit assessment A23-92 showed an indication of a non-quantifiable added benefit for patients with achondroplasia aged 2 years and older in whom the epiphyses are not yet closed. However, these patients differ considerably from those in the present research question. While the patient population of benefit assessment A23-92 (≥ 2 years) show a predominantly constant course of the annualized growth velocity, the patients in the present research question (≥ 4 months to < 2 years) are in a highly dynamic growth phase with a continuous decrease in the annualized growth velocity. Thus, a supplementary consideration of the evidence from benefit assessment A23-92 in the sense of a transfer to the patients of the present research question is not appropriate. Irrespective of this, there are also differences in the pharmacokinetics that lead to a higher dose in children < 2 years of age.



solid lines: children with achondroplasia; dashed lines: average children
average children and for children with achondroplasia
Jungen: boys
Mädchen: girls
Jährliche Wachstumsgeschwindigkeit: annualized growth velocity
cm pro Jahr: cm per year
Alter (Jahre): age (years)
Pubertärer Wachstumsschub fehlt bei Kindern mit Achondroplasie: No pubertal growth spurt in children with achondroplasia

Figure 1: Graphs from Module 3 A of the company on the annualized growth velocity for

Even if, in view of the principle of action of vosoritide, it seems plausible to start treatment as early as possible in order to enable a potential increase in growth over a maximum period of

time and thus an increased final height, the derivation of an added benefit is currently not supported by data.

In summary, there is no hint of an added benefit of vosoritide in comparison with the ACT BSC for patients aged 4 months to < 2 years with achondroplasia.

Table 3 shows a summary of the probability and extent of added benefit of vosoritide.

Table 3: Vosoritide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with achondroplasia[b] aged 4 months to < 2 years	BSC[c]	Added benefit not proven

a. Presented is the 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.

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

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report was to assess the added benefit of vosoritide in comparison with BSC as ACT in patients aged 4 months to < 2 years with achondroplasia.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of vosoritide

Therapeutic indication	**ACT[a]**
Patients aged 4 months to < 2 years with achondroplasia[b]	BSC[c]
a. Presented is the 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. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee	

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 52 weeks were used for deriving an added benefit. The company chose no restrictions regarding a minimum treatment duration or the study type for the evidence used by it. In addition, the company did not limit itself to patients aged between 4 months and < 2 years in accordance with the above-mentioned research question, but considered all patients in the therapeutic indication of vosoritide (from the age of 4 months in whom the epiphyses are not yet closed). In the dossier, under “Further investigations”, it also presented analyses that included results from non-randomized and non-comparative studies to show the long-term effects of vosoritide. See Section I 3.1 for information on the handling of the data presented under further investigations.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on vosoritide (status: 16 November 2023)
- bibliographical literature search on vosoritide (last search on 12 November 2023)
- search in trial registries/trial results databases for studies on vosoritide (last search on 12 November 2023)
- search on the G-BA website for vosoritide (last search on 16 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on vosoritide (last search on 18 December 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

In addition to the included study BMN 111-206 (hereinafter referred to as Study 206), the ongoing RCT BMN 111-209 [3] was identified as a basically relevant study, but the dossier contains no results. The study included children up to 12 months of age with achondroplasia and at an increased risk of requiring cervicomedullary decompression surgery. The included patients thus represent a subpopulation of the present research question, whereby it is assumed on the basis of the available information that the population investigated there does not overlap to a relevant extent with the patient population of the BMN 111 study-206 used for the benefit assessment. The European Public Assessment Report (EPAR) [4] lists an abridged interim report of the BMN 111-209 study for the assessment of the clinical safety. In the EPAR, these data are included in the analysis of a pooled safety population and are not available separately for the BMN 111-209 study. According to the study protocol, anthropometric measurements are also carried out, so that analyses of patient-relevant benefit outcomes in the present therapeutic indication such as height (z-score), are principally also conceivable (see Section I 4). In principle, therefore, a balancing of benefit and harm also appears possible for the population at an increased risk of requiring cervicomedullary decompression surgery considered in the BMN 111-209 study. However, according to the company, an interim analysis was only to be conducted after the 2-year randomized treatment phase although recruitment had been completed for the ongoing BMN 111 study-209.

Based on the information available, it is unclear whether the abridged interim report of the BMN 111-209 study described in the EPAR (interim report of 25 February 2022 for the assessment of the clinical safety) is a data cut-off requested by the regulatory authority. If the

data cut-off is requested by the regulatory authority, it is a data cut-off relevant for the benefit assessment. In this case, according to the dossier template, complete analyses for all patient-relevant outcomes recorded must be conducted and presented for all data cut-offs relevant for the benefit assessment.

Since the present assessment supplementarily considered single-arm long-term data of a vosoritide therapy, these were also checked for completeness. No additional relevant study was identified.

The company conducted no information retrieval for further investigations with the ACT.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
BMN 111-206 (206[c])	Yes	Yes	No	Yes [5,6]	Yes [7-9]	Yes [10]

a. Study for which the company was sponsor.
b. Citation of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

BSC: best supportive care; RCT: randomized controlled trial

The study pool for the benefit assessment of vosoritide in patients aged 4 months to < 2 years with achondroplasia comprises Study 206. Study 206 is already known from a previous benefit assessment procedure in which Cohort 1 of the study was used to assess the added benefit of vosoritide [11]. In contrast, the company considered the entire therapeutic indication of vosoritide (see Chapter I 2) and, in addition to Study 206, also included the RCT BMN 111-301 [12] in its study pool. This study only included patients from 5 years of age who were thus outside the age range of the present research question. Therefore, the study is not relevant for the present benefit assessment and is not considered further. A detailed description of the BMN 111-301 study can be found in dossier assessment A23-92 [11]. To assess the sustainability of the effects of vosoritide, partial results of the long-term data presented by the company are considered as supportive information (see following section).

Long-term data

In its dossier, the company presented various analyses to illustrate the long-term effects of treatment with vosoritide for the entire therapeutic indication (patients from 4 months of age in whom the epiphyses are not yet closed). Depending on the analysis, these include results on selected outcomes over the periods of the RCTs 206 and BMN 111-301 and their respective extension studies (BMN 111-208 [13] and BMN 111-302 [14]), the period of study BMN 111-202 [15] and its extension study BMN 111-205 [16] as well as over the period of the observational study BMN 111-901 [17] of at least 1 year, the RCT BMN 111-301 and the 1st treatment year of the extension study BMN 111-302.

Figure 2: Presentation of how the studies presented by the company are related presents an overview of the evidence and of the relation between the studies.

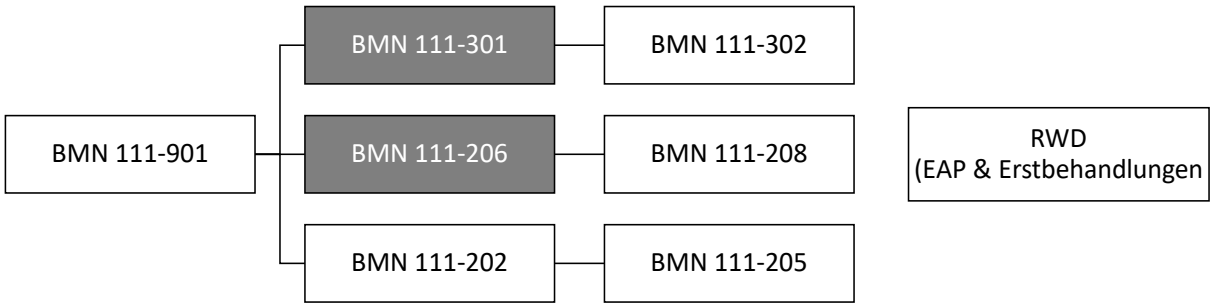


Figure 2: Presentation of how the studies presented by the company are related

shaded: RCT; not shaded: other study type; EAP: early access programme; RWD: real-world data

Erstbehandlungen: Initial treatments

A detailed description of the long-term data presented by the company can be found in dossier assessment A23-92 [11]. In comparison with Module 4 A of benefit assessment A23-92, the company presented new data cut-offs for the extension studies BMN 111-205, BMN 111-208 and BMN 111-302.

The relevant patient population of the present research question only includes patients aged 4 months to < 2 years with achondroplasia. Thus, only study BMN 111-208 is relevant for the supporting consideration of long-term effects of treatment with vosoritide as an extension study of Study 206 included in the assessment and is described again below.

BMN 111-208 study

Study characteristics

Patients who completed the placebo-controlled RCT 206 (see Section I 3.2 for a description) then had the opportunity to take part in the open-label extension study BMN 111-208 and

continue treatment with vosoritide there. A total of 73 patients were included in one of 4 age cohorts (age at first administration of vosoritide: 0 to < 6 months, ≥ 6 to < 24 months, ≥ 24 to < 60 months, ≥ 60 months). Observation is carried out until the child reaches near-final adult height (NFAH), defined as evidence of growth plate closure and an annualized growth velocity < 1.5 cm per year. For the ongoing study BMN 111-208, the company presents analyses for the outcomes of height (z-score), annualized growth velocity and upper to lower body segment ratio for the data cut-off of 19 December 2022. However, the graphical representations of the long-term data in Module 4 A show an older data cut-off (26 January 2022). For the body proportion ratios of the extremities, the company used the data cut-off of 26 January 2022.

Presented analyses on the relevant age group and handling in the benefit assessment

Table 6 shows an overview of the analyses presented by the company on the long-term data of vosoritide therapy in the relevant age group (4 months to < 2 years) over the period of studies 206 and BMN 111-208 (hereinafter referred to as 206/208).

Table 6: Overview of the analyses presented by the company on long-term data of Study 206 and the BMN 111-208 study for patients aged between 4 months and < 2 years at the 1st dose of vosoritide (multipage table)

Outcome analyses	**Comparative [yes/no]**	**External control group**	**Age of the patients[a] [months]**	**Period or time point[b] (of which informative[c])**	**Supporting consideration [yes/no]**
Annualized growth velocity [cm/year]					
Change from baseline	No (descriptive)	–	0 to < 6	3 years	No
			≥ 6 to < 24	3.5 years	No
Longitudinal analysis	Yes	CLARITY	0 to < 6	1 year	No
			≥ 6 to < 24	1 year	No
Height (z-score)					
Change from baseline (z-score compared with healthy CDC reference [18])	No (descriptive)	–	0 to < 6	3 years (2 years)	Yes
			≥ 6 to < 24	3.5 years (3.5 years)	Yes
Change from baseline (z-score versus achondroplasia reference [19])	No (descriptive)	–	0 to < 6	3 years	No
			≥ 6 to < 24	3.5 years	No
Longitudinal analysis (z-score compared with healthy CDC reference [18])	Yes	CLARITY	0 to < 6	1 year and 2 years	No
			≥ 6 to < 24	1, 2 and 3 years	No
Cross-sectional analysis (z-score compared with healthy CDC reference [18])	Yes	CLARITY	0 to < 6	1 year and 2 years	No
			≥ 6 to < 24	1, 2 and 3 years	No
Longitudinal analysis (z-score compared with healthy CDC reference [18])	Yes	Observation/placebo[d]	0 to < 6	1 year	No
			≥ 6 to < 24	1 year and 2 years	No
Longitudinal analysis (z-score compared with achondroplasia reference [19])	Yes	Observation/placebo[d]	0 to < 6	1 year	No
			≥ 6 to < 24	1 year and 2 years	No
Cross-sectional analysis (z-score compared with healthy CDC reference [18])	Yes	Observation/placebo[d]	0 to < 6	1 year and 2 years	No
			≥ 6 to < 24	1, 2 and 3 years	No

Table 6: Overview of the analyses presented by the company on long-term data of Study 206 and the BMN 111-208 study for patients aged between 4 months and < 2 years at the 1st dose of vosoritide (multipage table)

Outcome analyses	**Comparative [yes/no]**	**External control group**	**Age of the patients[a] [months]**	**Period or time point[b] (of which informative[c])**	**Supporting consideration [yes/no]**
Cross-sectional analysis (z-score compared with achondroplasia reference [19])	Yes	Observation/placebo[d]	0 to < 6	1 year and 2 years	No
			≥ 6 to < 24	1, 2 and 3 years	No
Upper to lower body segment ratio					
Change from baseline	No (descriptive)	–	0 to < 6	3 years	No
			≥ 6 to < 24	3.5 years	No
Longitudinal analysis	Yes	Observation/placebo	0 to < 6	1 year	No
			≥ 6 to < 24	1 year and 2 years	No
Cross-sectional analysis	Yes	Observation/placebo	0 to < 6	1 year and 2 years	No
			≥ 6 to < 24	1, 2 and 3 years	No
Body proportion ratios of the extremities[e]					
Change from baseline	No (descriptive)	–	0 to < 6	2 years	No
			≥ 6 to < 24[f]	2.5 years	No

a. Age cohort at the start of treatment with vosoritide. Analyses are also available for patients > 24 months at the time of the first administration of vosoritide, but these are not included in the present therapeutic indication.
b. Information provided by the company.
c. The informative time period is only specified for analyses that are considered as supportive information. No conclusions can be drawn for a longer period due to low patient numbers at the later documentation time points.
d. Combined prospective observational data from study BMN 111-901, pre-treatment data from Study 206 and data from the placebo arms of studies BMN 111-301 and 206.
e. Upper arm length to lower arm length, upper leg length to knee to heel length, upper leg length to tibial length, and arm span to standing height.
f. For Cohort 2 (≥ 6 to < 24 months), the company's Module 4 A did not include a separate analysis of the children who had already been treated with vosoritide in Study 206 (vos/vos arm).

CDC: Centers for Disease Control and Prevention; vos: vosoritide

Descriptive analyses

The analyses 206/208 comprise descriptively reported results for the total population, and separately for the respective age groups of 0 to < 6 months, 6 months to < 24 months, 24 to < 60 months, ≥ 60 months. In Module 4 A, the results of the respective age cohort are presented separately by the respective study arm of Study 206 and also overall (except for outcomes on body proportion ratios for the age group ≥ 6 to < 24 months, here only overall). In the separate presentation by study arm, a distinction was made as to whether the patients in Study 206 were in the intervention arm and continued to receive vosoritide in the extension study (vos/vos [incl. sentinels]) or whether they initially received placebo in Study 206 and only started treatment with vosoritide in Study BMN 111-208 (plc/vos). For the outcome of height (z-score), the company presented an analysis using a healthy US reference population according to the Centers for Disease Control and Prevention (CDC) as well as an analysis in comparison with an achondroplasia reference (for a more detailed description of the outcome of height [z-score], see Section I 4.1). Due to the present research question (age ≥ 4 months to < 2 years), the analyses with children aged 0 to < 6 months and those with children ≥ 6 to < 24 months are relevant for the supporting consideration of long-term effects in the outcome of height (z-score), and of these only the vos/vos arms without sentinels, as these represent a longer period with vosoritide administration. Analyses excluding the unblinded sentinel patients are not available.

Comparative analyses

As comparative analyses, the company presents different longitudinal and cross-sectional analyses on various outcomes compared to external control groups. An external control group was formed using data from the retrospective observational study CLARITY (also referred to as “ACH-NH” by the company) on the natural course of disease of achondroplasia patients [19]. As a further external control group, the company presented a comparison with combined prospective observational data from study BMN 111-901, pre-treatment data from Study 206 and data from the placebo arms of studies BMN 111-301 und 206 (observation/placebo) for the analysis 206/208.

For the longitudinal analyses against data from the CLARITY study, matching was performed by sex, age at baseline (actual age in months with 1 decimal place ± 1 month), height at baseline (± 5 cm) and height (z-score) at baseline (± 1 SDS). For the longitudinal analyses versus the prospective observational/placebo data, the company stated that no matching was performed due to too few participants with sufficient follow-up. For the cross-sectional analyses with the external controls from the CLARITY study and the observational/placebo data, the company stated that matching was performed separately for baseline and years 1, 2, 3 and 4 depending on age (actual age in months with 1 decimal place ± 1 month) and sex. In fact, due to limited data in the relevant age groups, the company did not conduct any cross-sectional analyses at all for year 4 and only partially for year 3.

The presented cross-sectional analyses versus external control arms are not suitable for the supporting consideration in the present benefit assessment, as the same patients were not observed over time in the control groups formed. The cross-section at baseline and the respective time of analysis can result in fundamentally different comparator populations. In the comparison 206/208 vs. CLARITY or observation/placebo, all children from Study 206 were included in the intervention arm 206/208 for the age group ≥ 6 to < 24 months, i.e. also those who had initially been treated with placebo in Study 206. Patients in the age group 0 to < 6 months who received placebo in Study 206 were also included in the age group ≥ 6 to < 24 months, as they transition to the older age group (≥ 6 to < 24 months) at the time of the 1st dose of vosoritide in study BMN 111-208. In addition, the sentinel patients who received unblinded vosoritide (see also Section I 3.2) are included in analysis 206/208 both in the age group 0 to < 6 months and in the age group ≥ 6 to < 24 months.

Notwithstanding the aforementioned points of criticism, the company did not conduct an information retrieval for further investigations with the ACT. The study pool is therefore potentially incomplete with regard to the ACT. For this reason, the longitudinal analyses are also not suitable for a supporting analysis.

Analyses considered

In summary, the descriptive analyses of the change from baseline (only the children who were in the intervention arm of Study 206 and continued treatment with vosoritide in study BMN 111-208) are considered to support the assessment of the added benefit in order to be able to assess possible effects of longer-term treatment with vosoritide (see Section I 5.2).

Analyses on the outcome of height (z-score) are considered in a supportive manner.

In order to enable better comparability of the long-term data between the different age cohorts in the therapeutic indication, it would also be useful (especially for z-score and AGV) to show the height z-scores in relation to the children’s age (on the x-axis).

In addition, results on the outcomes of annualized growth velocity, ratio of upper to lower body segment and body proportions of the extremities are presented in I Appendix F.

In its dossier, the company only presents tabular analyses for the outcomes height (z-score), annualized growth velocity and ratio of upper to lower body segment for the data cut-off of 19 December 2022. However, the graphical analyses presented in the dossier and the results on the outcome "body proportion ratios of the extremities" are based on an older data cut-off from 26 January 2022. If available, the results on the outcomes mentioned are presented as supplementary information in I Appendix F. Based on the company's result tables for the data cut-off of 19 December 2022, a separate graph was prepared for the outcome of height (z-score) (Figure 22). For the outcomes of annual growth velocity and ratio of upper to lower

body segment, which are only presented as supplementary information, the figures presented by the company for the older data cut-off of 26 January 2022 are shown in I Appendix F of the full dossier assessment (see Figure 24, Figure 25 and Figure 27).

I 3.2 Study characteristics

Table 7 and Table 8 describe the study used for the benefit assessment.

Table 7: Characteristics of the study included – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
206[b]	RCT, double-blind, parallel	Children with genetically confirmed achondroplasia aged 0 to < 60 months	Cohort 1[c] (children aged ≥ 24 to < 60 months): ▪ vosoritide[d] (N = 15) ▪ placebo (N = 16) cohort 2 (children aged ≥ 6 to < 24 months): ▪ vosoritide[d] (N = 8) ▪ placebo (N = 8) cohort 3 (children aged 0 to < 6 months): ▪ vosoritide[d] (N = 9) ▪ placebo (N = 8)	Screening: 4 weeks[e] Treatment: 52 weeks Observation period: 4 weeks[f]	16 centres in Australia, Japan, United Kingdom, United States 06/2018–01/2022	Primary: body length/height[g] based on z-scores, as well as AEs secondary: mortality, morbidity, health-related quality of life

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. In order to participate in Study 206, patients in Cohort 1 and 2 had to previously participate in the observational study BMN 111 901 for ≥ 6 months to record growth data. Growth data for Cohort 3 could be recorded over a 3-month period by participating in the observational study BMN 111-901 or directly in Study 206 (for children aged 0 to ≤ 3 months). Following Study 206, all eligible patients could continue treatment with vosoritide in the open-label extension study BMN 111-208. A total of 73 children transitioned to the open-label extension study.
c. This cohort is not relevant for the assessment and is no longer shown in the following tables. A comprehensive presentation of this cohort can be found in dossier assessment A23-92 [11].
d. Sentinel patients received open-label vosoritide and were monitored for 8 days to assess short-term safety and pharmacokinetics. The remaining patients were only included in the respective cohort after approval by the data monitoring committee. After completion of Week 12 of the corresponding sentinel patients and a review by the data monitoring committee, the sentinel patients of the next younger cohort were treated. Cohorts 1 and 2 each included 4 unblinded sentinel subjects, and 3 sentinel subjects were included in Cohort 3.
e. For patients in Cohort 3, a 3-month observation phase was conducted after screening to collect baseline growth data, unless these had already been collected in the observational study BMN 111-901.
f. The safety follow-up visit did not take place if the patient had transitioned to another vosoritide study or a registry within 4 weeks of the last dose.
g. Length was obtained in a supine position; height was measured standing up.

AE: adverse event; BSC: best supportive care; N: number of randomized patients; RCT: randomized controlled trial

Table 8: Characteristics of the intervention – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study	Intervention	Comparison
206	Vosoritide SC 30 µg/kg body weight[a], once daily	Placebo SC, once daily
	dose adjustments ▪ only for sentinel patients if there is a relevant difference between the AUC of the plasma concentration-time curve and the AUC of the 15 µg/kg cohort from the BMN 111-202 study	
	Disallowed pretreatment ▪ growth hormones, insulin-like growth factor 1, or anabolic steroids in the previous 6 months or for longer than 3 months ▪ hip surgery ▪ limb-lengthening surgery, surgery of the spine or long bones, or bone-related surgery and chronic complications ▪ new initiation of sleep apnoea treatment < 2 months prior to screening ▪ corticosteroids for ≥ 1 month in the previous 12 monthsb ▪ chronic therapy with antihypertensive medicationsb, c, GnRH agonists or any other medications that, in the opinion of the investigators, may affect the safety or ability to participate in this clinical study ▪ other investigational products or investigational medical devices (< 30 days prior to screening) for achondroplasia or short stature (at any time) ▪ drugs that prolong the QT/QTc interval (< 14 days or < 5 half-lives before the screening visit[b]) **allowed pretreatment** ▪ low-dose inhaled steroid for asthma, or intranasal steroids **disallowed concomitant treatment** ▪ planned limb-lengthening surgery **allowed concomitant treatment** ▪ additional drugs at the investigator's discretion	

a. Patients in Cohort 2 initially received 15 µg/kg vosoritide. After analysing the safety and pharmacokinetic data of the sentinel patients, the dose was increased to 30 µg/kg. At the visit that took place immediately before the patients' 2nd birthday, the dose was reduced to 15 µg/kg.
b. Applies to Cohort 3 already for participation in the 3-month observation phase.
c. Including ACE inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium channel blockers, cardiac glycosides and systemic anticholinergic agents.

ACE: angiotensin-converting enzyme; AUC: area under the curve; BSC: best supportive care; GnRH: gonadotropin-releasing hormone; RCT: randomized controlled trial; SC: subcutaneous

Study design and patient population

Study 206 is a phase 2, double-blind, 52-week RCT assessing vosoritide versus placebo in children aged 0 to < 5 years with genetically confirmed achondroplasia.

Patients included in Cohorts 1 (≥ 2 to < 5 years) and 2 (≥ 6 months to < 2 years) had to have completed a prior observation phase of at least 6 months in the BMN 111-901 study. In addition, this observation phase had to include a recording of body height or body length, which took place ≥ 6 months before screening of Study 206. Patients in Cohort 3 (0 to < 6 months) had to have completed an observation phase of at least 3 months, either by

participating in the BMN 111-901 study or as part of Study 206 (for children aged 0 to ≤ 3 months). Furthermore, no indication of cervicomedullary compression requiring surgery within 60 days of screening was allowed. In addition, planned spinal or limb-lengthening surgery, fracture of the long bones or spine within 6 months before screening, history of hip surgery or severe hip dysplasia, and severe untreated sleep apnoea led to exclusion from the study. A total of 75 patients were included.

In the beginning of the study, 4 sentinel patients in the oldest cohort (Cohort 1) were initially treated with open-label vosoritide to assess short-term safety and pharmacokinetics. After all sentinels had completed Day 8 of treatment, the cohort was opened to the remaining patients. Once the sentinels in the respective cohort had completed Week 12 of treatment, the short-term safety and pharmacokinetic data were assessed by the data monitoring committee. Subsequently, the sentinel patients in the next younger age cohort were treated with vosoritide in an analogue procedure. Four sentinel patients in Cohort 2, and 3 sentinel patients in Cohort 4 received open-label treatment with vosoritide. A total of 11 children in Study 206 received unblinded vosoritide.

Randomization was performed in a 1:1 ratio and was stratified by the characteristic of age within Cohorts 1 and 2 (≥ 24 to < 36 months versus ≥ 36 to < 60 months for Cohort 1, and ≥ 6 to < 15 months versus ≥ 15 to < 24 months for Cohort 2). In Study 206, a total of 32 patients were randomized to the intervention arm and 32 patients to the comparator arm.

In accordance with the randomization, patients in Cohort 1 received approval-compliant treatment with subcutaneous vosoritide 15 µg/kg once daily [20] or with subcutaneous placebo once daily. For patients in Cohort 2, the vosoritide dose was increased from the originally planned 15 µg/kg to 30 µg/kg after analysis of the pharmacokinetic data. The initial dose of Cohort 3 was 30 µg/kg [20] in compliance with the approval. Due to deviating dosing strategies in Study 206 (by weight and age) and the SPC (by weight), there are patient-specific deviations between the approval-compliant dose and the dose actually administered in the study. However, these deviations are irrelevant for the present benefit assessment. Due to the observation phase required in advance (see above), the patients included in Cohort 3 received the first dose of vosoritide at the earliest at the age of 4 months. In addition to the study medication, concomitant treatments were permitted at the discretion of the investigator. For information on the implementation of the ACT BSC, see the following section.

The primary outcome of Study 206 was the change in body length/height z-score as well as safety and tolerability. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, and health-related quality of life. Following Study 206, all eligible patients had the option to continue treatment with vosoritide in the open-label extension study BMN 111-208.

Relevant subpopulation of Study 206

In study 206, patients aged 0 to < 5 years were included in 3 different age cohorts. However, the present research question only comprises patients aged 4 months to < 2 years with genetically confirmed achondroplasia. Therefore, only the analyses for the relevant subpopulation are used for the benefit assessment. This includes patients of Cohort 2 (age ≥ 6 months to < 2 years, excluding sentinel patients) and Cohort 3 (age 0 to < 6 months, excluding sentinel patients). In Cohort 3, patients who were < 4 months at the time of study inclusion were also covered by this research question, as they were initially included in an observation phase, meaning that the patients were ≥ 4 months old when they received the first dose of vosoritide. Where possible and appropriate, Cohorts 2 and 3 were summarized in a meta-analysis (see Section "Meta-analysis of results"). This, therefore, comprised a total of 17 patients in the intervention arm and 16 in the comparator arm. Patients in Cohort 1 are not included in the present research question. A comprehensive presentation of this cohort can be found in dossier assessment A23-92 [11].

Implementation of the ACT BSC

The G-BA defined BSC as ACT. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. There are no high-quality guidelines for the treatment of achondroplasia. For Germany, for example, there is currently only a general S1 guideline on short stature [21]. There are also European and international consensus statements on achondroplasia [22,23].

In general, patients with achondroplasia may have various complications, including in particular restrictive pulmonary disease, infections, sleep apnoea, otitis media, cervicomedullary compression, musculoskeletal manifestations leading to chronic pain, e.g. bow legs and cardiovascular diseases [23]. Consequently, a BSC includes appropriate therapies for the treatment of possible complications (drugs, any necessary surgery, physiotherapy). In addition, the shorter stature and the different body proportion ratios compared with normal body growth result in a need for aids to improve aspects of daily living [22], especially in older patients than those of the present research question. The current general German S1 guideline on short stature also points out that child psychological support may be useful [21].

According to the inclusion and exclusion criteria of Study 206, children with planned spinal surgery, limb-lengthening surgery, or surgery for cervicomedullary compression during the study period were excluded from participation in the study. In addition, the presence of severe untreated sleep apnoea immediately before starting treatment with vosoritide was not allowed. However, this does not rule out the possibility that, in case of need, appropriate treatment was initiated or carried out during the course of the study.

The use of drugs during the course of the study was generally permitted in Study 206. In the comparator arm, 50% of the children in Cohort 2 and 88% of the children in Cohort 3 received an analgesic during the course of the study. Systemic administration of antibacterial drugs was also initiated in 50% of the children in Cohort 2 and 50% of the children in Cohort 3 in the comparator arm. There were only restrictions with regard to a few drugs and therapies, including, for example, antihypertensive medications or the disallowed use of GnRH agonists (see also Table 8). With regard to antihypertensive therapies, however, the children included in the study were not allowed to have any cardiovascular disease at the start of the study per inclusion and exclusion criteria. If antihypertensive therapy was initiated, treatment with the study medication had to be discontinued. However, in Study 206, this did not apply to any patient. In Germany, GnRH agonists are not approved for the treatment of achondroplasia and are also not mentioned in the German S1 guideline [21]. Since growth hormones are not a useful therapeutic approach for genetic achondroplasia, prohibiting these drugs is not a relevant restriction of the ACT. Likewise, limb-lengthening surgery is not a regularly performed treatment option in the German health care context. Taking into account the available information, the ACT BSC is overall considered to be adequately implemented.

Characteristics of the study population

Table 9 shows the characteristics of the patients in Cohort 2 or Cohort 3 of the included Study 206.

Table 9: Characteristics of the study populations as well as study/therapy discontinuation – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Cohort characteristic category	Cohort 2 (≥ 6 to < 24 months)		Cohort 3 (0 to < 6 months)	
	vosoritide + BSC	placebo + BSC	vosoritide + BSC	placebo + BSC
	N[a] = 8	N[a] = 8	N[a] = 9	N[a] = 8
Study 206				
Age [months], mean (SD)	17.0 (5.8)	16.9 (6.2)	5.6 (0.4)	5.8 (0.6)
Sex [F/M], %	38/63	38/63	44/56	88/13
Family origin, n (%)				
White	6 (75)	6 (75)	7 (78)	6 (75)
Asian	2 (25)	1 (13)	2 (22)	2 (25)
Native Hawaiians or other Pacific Islanders	0 (0)	1 (13)	0 (0)	0 (0)
Body weight [kg], mean (SD)	9.0 (1.3)	8.4 (2.0)	5.9 (0.7)	6.4 (0.7)
Height (z-score)[b], mean (SD)	-3.4 (0.8)	-4.2 (1.2)	-3.3 (1.0)	-2.7 (0.8)
Height [cm], mean (SD)	69.2 (5.6)	66.5 (6.7)	57.7 (1.9)	58.2 (2.8)
Annualized growth velocity [cm/year], mean (SD)	11.5 (4.7)	10.6 (4.8)	21.2 (2.8)	19.5 (7.6)
Upper to lower body segment ratio, mean (SD)	2.7 (0.3)	2.7 (0.3)	3.0 (0.5)	2.9 (0.2)
Arm span to standing height ratio, mean (SD)	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)
Upper arm length to lower arm length ratio, mean (SD)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.0 (0.1)
Upper leg length to knee to heel length ratio, mean (SD)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.6 (0.1)
Upper leg length to tibial length ratio, mean (SD)	1.2 (0.1)	1.1 (0.2)	1.1 (0.1)	1.0 (0.3)
Treatment discontinuation, n (%)	0 (0)	1 (13)	1 (11)	0 (0)
Study discontinuation, n (%)	0 (0)	1 (13)	1 (11)	0 (0)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Discrepancies within Module 4 A and between Module 4 A and study documents. Age- and sex-adjusted numbers of standard deviations (z-scores) were determined against a US reference population (CDC reference) of average stature (data according to Module 4 A, Table 4-17, and study report).

BSC: best supportive care; CDC: Centers for Disease Control and Prevention; f: female; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics within the relevant cohorts of Study 206 are largely balanced between the intervention and the comparator arm. In both relevant cohorts, the majority of patients were of white family origin. With 63%, Cohort 2 included more boys, while Cohort 3

included more girls. A clear difference in the sex distribution is shown in the comparator arm of Cohort 3 (88% girls vs. 13% boys). Since the cohorts were categorized by the characteristic of age, Cohort 3 comprised younger patients with a mean age of 5.6 months in the intervention arm and 5.8 months in the comparator arm. The mean age in Cohort 2 was about 17 months.

The growth velocity in Cohort 3 was approximately twice as high as in Cohort 2. The younger patients in Cohort 3 showed a smaller deviation in height from the healthy reference population of the Center for Disease Control and Prevention (CDC) than the older patients in Cohort 2. However, taking into account the natural growth process in children, the two aspects described above are plausible. There were also differences in body height z-scores within the individual cohorts. The mean z-score in Cohort 2 was -3.4 in the intervention arm and -4.2 in the comparator arm. This means that the deviation in body height compared to the US reference population was less pronounced in the intervention arm than in the comparator arm. In Cohort 3, the z-score was -3.3 in the intervention arm and -2.7 in the comparator arm, meaning that achondroplasia was more pronounced in patients in the intervention arm in this cohort than in the comparator arm. At the start of the study, the body proportion ratios were largely balanced across both cohorts. With regard to the upper to lower body segment ratio, the patients in Cohort 2 (mean 2.7) showed lesser disproportionality compared with the patients in Cohort 3 (mean 3.0 or 2.9).

In both the comparator arm of Cohort 2 and the intervention arm of Cohort 3, 1 patient discontinued treatment and the study.

Meta-analytical summary of results

Study 206 included patients aged 0 to < 5 years. However, the present research question only comprised patients with achondroplasia aged 4 months to < 2 years. The relevant subpopulation thus comprised Cohorts 2 (≥ 6 months to < 2 years) and 3 (0 to < 6 months) of Study 206. Where possible and appropriate, Cohorts 2 and 3 were summarized in a meta-analysis. Forest plots of the meta-analysis are presented in I Appendix D of the full dossier assessment.

In contrast, as already described in Chapter I 2, the company does not address the present research question in its dossier, but the entire therapeutic indication of vosoritide, which comprises patients ≥ 4 months in whom the epiphyses are not yet closed [20]. In its analyses, the company considered both the entirety of Study 206 (Cohorts 1 to 3) and the individual cohorts. A summarized analysis of Cohorts 2 and 3 is not available.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
206	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for Study 206.

Transferability of the study results to the German health care context

The company stated that, worldwide, achondroplasia is largely caused by the same mutation in the fibroblast growth factor receptor 3 (FGFR3) and shows minor inter-individual differences. The company therefore assumed that the results of the international studies are transferable to everyday health care in Germany. The company further stated that the results of the BMN 111-301 study (patients aged ≥ 5 to < 18 years who do not fall under the present research question) for the height z-score based on a German or European reference population compared with the results of the height z-scores based on a US reference population confirm excellent transferability of the studies.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - height (z-score)
  - upper to lower body segment ratio
  - body proportion ratios of the extremities (upper arm length to lower arm length, upper leg length to knee to heel length, upper leg length to tibial length, and arm span to standing height)
  - functional independence (WeeFIM)
- Health-related quality of life
  - infant Toddler Quality of Life Questionnaire (ITQOL)
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - injection site reactions (High Level Term [HLT], AE)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used other outcomes in the dossier (Module 4 A).

Table 11 shows the outcomes for which data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study	Outcomes										
	All-cause mortality[a]	Height (z-score)	Upper to lower body segment ratio	Body proportion ratios of the extremities[b]	Functional independence (WeeFIM)	Health-related quality of life (ITQoL)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Injection site reactions (HLT, AEs)	Other specific AEs
206	Yes	Yes	No[d]	No[d]	Yes[e]	No[d]	Yes[f]	Yes[f]	Yes	Yes	No[g]

a. Deaths were recorded as AEs.
b. Upper arm length to lower arm length, upper leg length to knee to heel length, upper leg length to tibial length, and arm span to standing height.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. No suitable data available, see body of text below.
e. The WeeFIM was not recorded in patients < 6 months, so no suitable data are available for Cohort 3 (0 to < 6 months) due to missing values at baseline.
f. Includes potentially disease-related events; however, it is assumed in the present data situation that this has no relevant influence on the results of the overall rates.
i. No other specific AEs were identified based on the AEs occurring in the relevant studies.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; HLT: High Level Term; ITQOL: Infant Toddler Quality of Life Questionnaire; RCT: randomized controlled trial; SAE: serious adverse event; WeeFIM: Pediatric Functional Independence Measure II

Notes on outcomes

Height (z-score)

Z-scores for height are derived using age and sex-specific reference data for children of average stature. The data were presented as z-scores (number of standard deviations) above or below the age-specific reference. The reference corresponds to a z-score of 0. Short stature is defined as a height deficit of at least 2.0 standard deviations below the population-specific mean height for age and sex, corresponding to a z-score of −2.

The company's dossier contains discrepant information on the reference population on which the derivation of the body height z-scores for Cohorts 2 and 3 of Study 206 was based. In Module 4 A, the company states that the z-scores for patients aged < 24 months are derived on the basis of body length compared to a reference from the World Health Organisation (WHO). However, in its analyses, the company presents results for Cohorts 2 and 3 of Study 206 that are based on body height z-scores derived from a CDC reference population [18].

In the present therapeutic indication of achondroplasia, height (z-score) is classified as patient-relevant. However, it is difficult to estimate how a specific change in the outcome of

height (z-score) will ultimately affect the patient. For the present benefit assessment, a (potential) added benefit in the outcome of height (z-score) can therefore not be conclusively quantified.

In Module 4 A, the company also presents analyses on the outcome of height (z-score) based on a German reference population for study BMN 111-301, which is not relevant in the present research question. However, these differ only slightly from the analyses based on the US reference population (CDC). In principle, however, the German reference population is the more relevant one and therefore preferable to a comparison with a US reference population (CDC) or a global reference population (WHO). However, analyses against a German reference population are not available for Study 206.

Annualized growth velocity

The annualized growth velocity is not assessed as patient-relevant per se. The outcome of height (z-score) is used for the present benefit assessment. Since an increased annualized growth velocity results directly in an increase in height, this is adequately covered by the outcome of height (z-score). The annualized growth velocity is therefore presented as supplementary information.

Upper to lower body segment ratio and body proportion ratios of the extremities

The upper to lower body segment ratio and body proportion ratios of the extremities (upper arm length to lower arm length, upper leg length to knee to heel length, upper leg length to tibial length, and arm span to standing height) are classified as patient relevant in the present therapeutic indication of achondroplasia. The data from the observational study BMN 111-901 show that a large proportion of patients in the RCT 206 already showed disproportionality of upper to lower body segments or extremities at baseline. The company considered the change from baseline in the corresponding body proportions and derived an added benefit of vosoritide based on no further change in body proportions (proportionate growth) (no statistically significant or clinically relevant differences were found between the 2 treatment arms). However, the operationalization presented is not informative. A meaningful interpretation of the treatment effect on the disproportionality of the patients requires a comparison of the body proportions versus a suitable healthy reference population, similar to the outcome of height (z-score). The operationalization of the outcomes of upper to lower body segment ratio and body proportion ratios of the extremities presented by the company are therefore not used to derive the added benefit. The results of the company are presented as supplementary information in I Appendix E of the full dossier assessment, however. The analyses of the company do not suggest a relevant effect of vosoritide treatment on the disproportionality.

Note on presented analyses of the instruments on morbidity and health-related quality of life used by the company

The company presented only continuous analyses for the instruments included in the present benefit assessment (WeeFIM and 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. The additional continuous analyses on the WeeFIM and ITQOL instruments conducted for the dossier lack information on the model or p-value. Therefore, the Institute conducted its own calculations for the present benefit assessment.

Functional independence (WeeFIM)

The WeeFIM is an instrument for assessing the functional independence of children (6 months to 7 years) with developmental disorders or special needs from the perspective of parents or carers. The WeeFIM consists of 18 items, which are assigned to the 3 domains of self-care, mobility and cognition. A total score is also calculated. The items represent the child's degree of dependency on a 7-level scale. A score of 7 indicates the child's complete independence, and decreases according to the need for support to a value of 1, which represents complete dependence in the corresponding situation. For the total score, this results in a scale range of 18 to 126, with higher values indicating better functional independence [24]. The instrument queries the current point in time. In Study 206, the company recorded the WeeFIM at screening, at Week 26, at Week 52 and at premature study discontinuation. Cohorts 2 and 3 of Study 206 are relevant for the present research question. As the WeeFIM is only recorded from the age of 6 months, no suitable data are available for patients in Cohort 3 (0 to < 6 months) due to a lack of baseline surveys. A meta-analysis of Cohorts 2 and 3 is not possible. A possible added benefit based on the WeeFIM can therefore only be derived for the age group ≥ 6 months to < 2 years (Cohort 2).

Infant Toddler Quality of Life Questionnaire (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 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, the subscales of behaviour, general behaviour, getting along with others and change in health cover a reference period of 1 year. Accordingly, these subscales 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 [25]. In the study, the ITQOL was recorded at baseline, Week 26, Week 52 and at premature study discontinuation.

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.

As described above, the subscales of behaviour, general behaviour, getting along with others and change in health were only recorded from the age of ≥ 12 months. Thus, no suitable data are available for Cohort 3 (0 to < 6 months) of Study 206 due to the lack of a baseline survey. In Cohort 2, there were also no baseline surveys available for patients aged ≥ 6 to ≤ 12 months at the start of the study. However, it is unclear what proportion of patients in Cohort 2 were not considered in the analyses due to their age. As the available information does not allow to adequately assess whether the criteria regarding the proportion of patients included in the analysis as a whole or regarding the difference in the proportions of patients between the treatment groups included in the analysis are met, no suitable data are available for these subscales for Cohort 2 of Study 206. In addition, no suitable data are available for the subscale on general health, which can be recorded from 2 months depending to the instrument, 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.

The results of the ITQOL are therefore not used for the benefit assessment. However, the results are presented as supplementary information in I Appendix E of the full dossier assessment. There are no statistically significant differences in the subscales for which suitable data are available.

SAEs and severe AEs

The analyses of the overall rates of SAEs and severe AEs potentially include events that can be attributed to the symptoms of the underlying disease. To allow an adequate assessment of side effects, however, the overall rates of SAEs and severe AEs must also be analysed excluding disease-related events. However, it is assumed in the present data situation that this has no relevant influence on the results on the overall rates.

I 4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Study	Study level	Outcomes										
		All-cause mortality[a]	Height (z-score)	Upper to lower body segment ratio	Body proportion ratios of the extremities[b]	Functional independence (WeeFIM)	Health-related quality of life (ITQOL)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Injection site reactions (HLT, AEs)	Other specific AEs
206	L	L	L	–[d]	–[d]	H[e]	–[d]	L[f]	L[f]	L	L	–

a. Deaths were recorded as AEs.
b. Upper arm length to lower arm length, upper leg length to knee to heel length, upper leg length to tibial length, and arm span to standing height.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. No suitable data available; for the reasoning, see Section I 4.1 of the present dossier assessment.
e. High proportion of patients not included in the analysis (> 10%) or large difference between the treatment groups (> 5 percentage points); no suitable data are available for the WeeFIM instrument for Cohort 3 (see Section I 4.1).
f. Includes potentially disease-related events; however, in the present data situation it is assumed that this has no relevant influence on the results on the overall rates.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; H: high; HLT: High Level Term; ITQOL: Infant Toddler Quality of Life Questionnaire; L: low; RCT: randomized controlled trial; SAE: serious adverse event; WeeFIM: Pediatric Functional Independence Measure II

Due to the high proportion (> 10%) of patients who were not considered in the analysis, and the large differences between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis, the results for the outcome "functional independence" (WeeFIM) have a high risk of bias for Cohort 2. For Cohort 3, no suitable data are available for the outcome of functional independence (WeeFIM). Overall, there are no suitable data available for the outcomes "ratio of upper to lower body segment", "body proportions of the extremities" and "health-related quality of life", recorded with the ITQOL. The risk of bias for all other outcomes was rated as low.

The available information allows deriving no more than a hint, e.g. of an added benefit, for the outcome of functional independence (WeeFIM). At most indications, e.g. of an added benefit, can be determined for all other outcomes for which suitable data are available.

I 4.3 Results

Table 13 and Table 14 summarize the results on the comparison of vosoritide + BSC with placebo + BSC in patients aged 4 months to < 2 years with achondroplasia.

If possible and meaningful, the present benefit assessment used the results of Cohorts 2 and 3 of Study 206 pooled in a meta-analysis. Forest plots of the meta-analyses calculated by the Institute can be found in I Appendix D of the full dossier assessment. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 13: Results (mortality and side effects) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Outcome category outcome cohort	Vosoritide + BSC		Placebo + BSC		Vosoritide + BSC vs. placebo + BSC
	N[a]	patients with event n (%)	N[a]	patients with event n (%)	RR [95% CI]; p-value[b]
Study 206					
Mortality					
All-cause mortality[c]					
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
Side effects					
AEs (supplementary information)[d]					
Cohort 2	8	8 (100.0)	8	8 (100.0)	–
Cohort 3	9	9 (100.0)	8	8 (100.0)	–
SAEs[d]					
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[e]
Severe AEs,[d, f]					
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)	–
Injection site reactions (HLT, AEs)[g]					
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[e]

Table 13: Results (mortality and side effects) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Outcome category outcome cohort	Vosoritide + BSC		Placebo + BSC		Vosoritide + BSC vs. placebo + BSC
	N[a]	patients with event n (%)	N[a]	patients with event n (%)	RR [95% CI]; p-value[b]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [26]). In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
c. Deaths were recorded as part of the AEs.
d. Including potentially disease-related events; in the present data situation, it is assumed that this does not have a relevant influence on the results for SAEs and severe AEs.
e. Institute's calculation: meta-analysis with fixed effect (Mantel-Haenszel method).
f. Operationalized as CTCAE grade ≥ 3.
g. The most common PTs in both cohorts were erythema at the injection site and reactions at the injection site.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; HLT: High Level Term; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 14: Results (morbidity) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

Outcome category outcome cohort	Vosoritide + BSC			Placebo + BSC			Vosoritide + BSC vs. placebo + BSC
	N[a]	values at baseline mean (SD)	change at Week 52 LS mean [95% CI]	N[a]	values at baseline mean (SD)	change at Week 52 LS mean [95% CI]	MD [95% CI]; p-value
Study 206							
Morbidity							
Height (z-score)[b]							
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]
Annualized growth velocity [cm/year], (supplementary information)							
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]*
Upper to lower body segment ratio							
Cohort 2	No suitable data[g]						
Cohort 3	No suitable data[g]						
Body proportion ratios of the extremities[h]							
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							
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]						

Table 14: Results (morbidity) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

Outcome category outcome cohort	Vosoritide + BSC			Placebo + BSC			Vosoritide + BSC vs. placebo + BSC
	N[a]	values at baseline mean (SD)	change at Week 52 LS mean [95% CI]	N[a]	values at baseline mean (SD)	change at Week 52 LS mean [95% CI]	MD [95% CI]; p-value
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							
ITQOL							
Cohort 2	No suitable data[g]						
Cohort 3	No suitable data[g]						

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Discrepant information between Module 4A and study documents, analysis based on a WHO reference population (information according to Module 4A)
c. LS means and difference in LS means from ANCOVA with the covariables of treatment, sex, age stratum, baseline age, baseline AGV, and baseline height z-score.
d. According to the company, based on 10 imputed data sets, but it is unclear what the company means by data sets. The sensitivity analyses presented in Module 4 A show that missing values of a patient were imputed.
e. Institute's calculation; meta-analysis with fixed effect (method with inverse variance).
f. LS means and difference in LS means from ANCOVA with the covariables of treatment, sex, age stratum, baseline age, and baseline AGV.
g. No suitable data are available; for further explanation see Section I 4.1. A supplementary presentation of the data submitted by the company can be found in I Appendix E.1.
h. Upper arm length to lower arm length, upper leg length to knee to heel length, upper leg length to tibial length, and arm span to standing height.
i. Higher (increasing) values indicate better functional independence; positive effects (intervention minus control) indicate an advantage for the intervention (scale range of total score: 18 to 126).
j. Mean (SD).
k. Effect, CI and p-value: Institute's calculation (t-test).
l. The WeeFIM was not recorded in patients < 6 months, so no suitable data are available for Cohort 3 (0 to < 6 months) due to missing values at baseline.

AGV: annualized growth velocity; ANCOVA: analysis of covariance; BSC: best supportive care; CI: confidence interval; ITQOL: Infant Toddler Quality of Life Questionnaire; LS: least squares; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; WeeFIM: Pediatric Functional Independence Measure II; WHO: World Health Organisation

The available information allows deriving no more than a hint for the outcome of functional independence (WeeFIM), and no more than an indication, e.g. of an added benefit, can be derived for all other outcomes (see also Section I 4.2).

Mortality

All-cause mortality

No deaths occurred in Cohort 2 of study 206. There was no significant difference between treatment groups in Cohort 3. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Height (z-score)

For the outcome of height (z-score), the meta-analysis of Cohorts 2 and 3 of Study 206 did not show any significant differences between treatment groups. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Due to the limited time period and the limited number of patients, the analyses of the long-term data on the outcome of height (z-score) presented by the company are currently not sufficient to assess the long-term effect of vosoritide at an early start of treatment (younger than 2 years) (see Section I 5.2).

A presentation of the long-term data can be found in I Appendix F of the full dossier assessment.

Upper to lower body segment ratio and body proportion ratios of the extremities

No suitable data are available for the outcomes of upper to lower body segment ratio and body proportion ratios of the extremities (see Section I 4.1). 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.

Functional independence (WeeFIM)

In Study 206, the WeeFIM was only recorded from the age of 6 months. For Cohort 3 (0 to < 6 months), therefore, no suitable data are available to assess the functional independence. For Cohort 2 (≥ 6 months to < 2 years), there was no significant difference between the treatment groups for the outcome of functional independence, recorded using WeeFIM. There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

ITQOL

No usable data are available for health-related quality of life, recorded using the ITQOL (for reasons, see Section I 4.1). There is no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, the meta-analysis of Cohorts 2 and 3 of Study 206 did not show any significant differences between treatment groups. There is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Severe AEs

In Cohort 2 of Study 206, there were no events in the outcome of severe AEs. There was no significant difference between treatment groups in Cohort 3. In each case, there is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", there were no events in either Cohort 2 or Cohort 3 of Study 206. There is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Injection site reactions (AE)

For the outcome of injection site reactions (AE), the meta-analysis of Cohorts 2 and 3 of Study 206 showed a significant difference between treatment groups to the disadvantage of vosoritide. This difference was no more than marginal, however. There is no hint of greater or lesser harm from vosoritide + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The present subgroup characteristic is relevant in the present benefit assessment.

- sex (male versus female)

There are no data available that allow a consideration of the subgroup characteristic "sex" (male vs. female) for the meta-analytical summary of Cohorts 2 and 3 of Study 206.

Basically, the subgroup characteristic of age is also relevant for the benefit assessment. In Study 206, the only prespecified subgroup characteristic was age, according to which the 3 cohorts were formed. Cohorts 2 and 3 of Study 206 are relevant for the present benefit assessment. In its dossier, however, the company only presents further post hoc specified subgroup analyses for the entirety of Study 206 and for Cohort 1. For the relevant subpopulation (patients from 4 months to < 2 years), no analyses on meaningful cut-off values are available for the characteristic "age".

In the present therapeutic indication, the subgroup characteristic of height (z-score) at baseline is suitable to depict disease severity. However, it is unclear whether the limits chosen by the company (≤ -4 vs. > -4) are reasonable.

Therefore, the subgroup characteristics of baseline height (z-score) and age are not used in the present benefit assessment.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 15).

Table 15: Extent of added benefit at outcome level: vosoritide + BSC vs. BSC (multipage table)

Outcome category **outcome**	**Vosoritide + BSC vs. BSC** **proportion of events (%) or mean change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality		
Cohort 2	0% vs. 0% RR: –	Lesser/added benefit not proven
Cohort 3	11.1% vs. 0% RR: 2.70 [0.13; 58.24]; p = 0.522	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Height (z-score)	−0.68 to 0.02 vs. −0.91 to −0.19[c] MD: 0.22 [-0.22; 0.66]; p = 0.332	Lesser/added benefit not proven
Upper to lower body segment ratio	No suitable data[d]	Lesser/added benefit not proven
Body proportion ratios of the extremities	No suitable data[d]	Lesser/added benefit not proven
Functional independence (WeeFIM)		
Cohort 2	14.7 vs. 16.2 MD: -1.50 [-22.41; 19.41]; p = 0.877	Lesser/added benefit not proven
Cohort 3	No suitable data[e]	Lesser/added benefit not proven
Health-related quality of life		
ITQOL	No suitable data[d]	Lesser/added benefit not proven
Side effects		
SAEs[f]	0% to 22.2% vs. 25.0% to 37.5%[c] RR: 0.42 [0.11; 1.60]; p = 0.203	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)[f]		
Cohort 2	0% vs. 0% RR: –	Greater/lesser harm not proven
Cohort 3	22.2% vs. 37.5% RR: 0.59 [0.13; 2.70]; p = 0.629	Greater/lesser harm not proven

Table 15: Extent of added benefit at outcome level: vosoritide + BSC vs. BSC (multipage table)

Outcome category outcome	Vosoritide + BSC vs. BSC proportion of events (%) or mean change effect estimation [95% CI]; p-value probability[a]	Derivation of extent[b]
Discontinuation due to AEs		
Cohort 2	0% vs. 0% RR: –	Greater/lesser harm not proven
Cohort 3	0% vs. 0% RR: –	Greater/lesser harm not proven
Injection site reactions (AE)	100.0% vs. 50% to 75% RR: 1.54 [1.06; 2.26]; RR: 0.65 [0.44; 0.94][g]; p = 0.025	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[h]

a. Probability provided if statistically significant and relevant differences are present.
b. Depending on the outcome category and the scale level of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Minimum and maximum proportions of events or mean changes in each treatment arm in the included cohorts of the study.
d. No suitable data are available for this outcome, see Section I 4.1 for justification.
e. The WeeFIM was only recorded from the age of 6 months. No suitable data are available for Cohort 3 due to a lack of baseline surveys.
f. Including potentially disease-related events; in the present data situation, it is assumed that this does not have a relevant influence on the results.
g. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
h. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_L: lower limit of the confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ITQOL: Infant Toddler Quality of Life Questionnaire; MD: mean difference; RR: relative risk; SAE: serious adverse event; WeeFIM: Pediatric Functional Independence Measure II

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of vosoritide in comparison with BSC

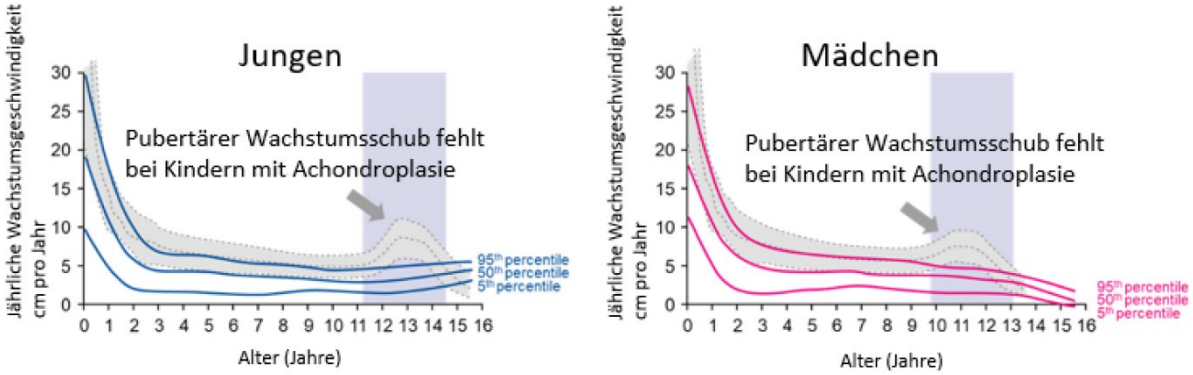
Positive effects	**Negative effects**
–	–
For Cohorts 2 and 3, there are no suitable data available for the outcomes “ratio of upper to lower body segment”, “body proportions of the extremities” and “health-related quality of life” (ITQOL). No suitable data are available for the outcome of functional independence (WeeFIM) in children aged < 6 years.	
BSC: best supportive care; WeeFIM: Pediatric Functional Independence Measure II	

For patients aged 4 months to < 2 years with achondroplasia, the results of Study 206 did not provide any hint of a lesser benefit or added benefit of vosoritide compared with the ACT BSC.

Overall, the evidence available from Study 206 and study BMN 111-208 for the age group ≥ 4 months to < 2 years comprises only a few patients (vosoritide 17 vs. placebo 16) and is therefore limited.

In particular, the long-term data from the BMN 111-208 study are currently not sufficient to assess the long-term effect of vosoritide at an early start of treatment (younger than 2 years). Currently, there are only limited data available covering a period of 3.5 years (maximum meaningful period: Cohort 2 = 3.5 years; Cohort 3 = 2 years) for up to 23 patients.

Benefit assessment A23-92 [11] showed an indication of a non-quantifiable added benefit for patients with achondroplasia aged 2 years and older in whom the epiphyses are not yet closed. However, these patients differ considerably from those in the present research question. While the patient population of benefit assessment A23-92 (≥ 2 years) showed a predominantly constant course of the annualized growth velocity, the patients of the present research question (≥ 4 months to < 2 years) were in a highly dynamic growth phase with a continuous decrease in the annualized growth velocity (see Figure 3). Thus, a supplementary consideration of the evidence from benefit assessment A23-92 in the sense of a transfer to the patients of the present research question is not appropriate. Irrespective of this, there are also differences in the pharmacokinetics that lead to a higher dose in children < 2 years of age.



solid lines: children with achondroplasia; dashed lines: average children
Jungen: boys
Mädchen: girls
Jährliche Wachstumsgeschwindigkeit: annualized growth velocity
cm pro Jahr: cm per year
Alter (Jahre): age (years)
Pubertärer Wachstumsschub fehlt bei Kindern mit Achondroplasie: No pubertal growth spurt in children with achondroplasia

Figure 3:Graphs from Module 3 A of the company on the annualized growth velocity for average children and for children with achondroplasia

Even if, in view of the principle of action of vosoritide, it seems plausible to start treatment as early as possible in order to enable a potential increase in growth over a maximum period of time and thus an increased final height, the derivation of an added benefit is currently not supported by data.

In summary, there is no hint of an added benefit of vosoritide in comparison with the ACT BSC for patients aged 4 months to < 2 years with achondroplasia.

Table 17 summarizes the result of the assessment of added benefit of vosoritide in comparison with the ACT.

Table 17: Vosoritide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with achondroplasia[b] aged 4 months to < 2 years	BSC[c]	Added benefit not proven

a. Presented is the 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.

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

The assessment described above differs from that of the company, which did not address the research question of the present benefit assessment (age ≥ 4 months to < 2 years) to assess the added benefit, but considered the entire therapeutic indication of vosoritide (patients aged ≥ 4 months in whom the epiphyses are not yet closed). Based on the RCTs BMN 111-206 and BMN 111-301 and the long-term data presented, the company initially claimed a minor added benefit for patients aged 4 months to < 5 years and a major added benefit for patients aged 5 to < 18 years. In its overall assessment, however, the company derived an indication of major added benefit regardless of age.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. BioMarin Pharmaceutical. A Clinical Trial to Evaluate Safety of Vosoritide in At-risk Infants With Achondroplasia [online]. 2023 [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT04554940.

4. European Medicines Agency. Voxzogo; Assessment report [online]. 2023 [Accessed: 14.02.2024]. URL: https://www.ema.europa.eu/en/documents/variation-report/voxzogo-h-c-005475-ii-0006-epar-assessment-report-variation_en.pdf.

5. BioMarin. Studienbericht BMN 111-206 - A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months. 2022.

6. BioMarin. A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months; study 111-206; Zusatzanalysen [unpublished]. 2023.

7. BioMarin Pharmaceutical. A Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children With Achondroplasia [online]. 2022 [Accessed: 09.01.2023]. URL: https://clinicaltrials.gov/study/NCT03583697.

8. BioMarin Pharmaceutical. A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months [online]. [Accessed: 09.01.2024]. URL: https://jrct.niph.go.jp/latest-detail/jRCT2080224833.

9. BioMarin Pharmaceutical. A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months [online]. [Accessed: 09.01.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003826-18.

10. Savarirayan R, Wilcox WR, Harmatz P et al. Vosoritide therapy in children with achondroplasia aged 3-59 months: a multinational, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Child Adolesc Health 2024; 8(1): 40-50. https://doi.org/10.1016/S2352-4642(23)00265-1.

11. 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.

12. Savarirayan R, Tofts L, Irving M et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. Lancet 2020; 396(10252): 684-692. https://doi.org/10.1016/S0140-6736(20)31541-5.

13. BioMarin Pharmaceutical. An Extension Study to Evaluate Safety and Efficacy of BMN 111 in Children With Achondroplasia [online]. 2023 [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT03989947.

14. BioMarin Pharmaceutical. An Extension Study to Evaluate the Efficacy and Safety of BMN 111 in Children With Achondroplasia [online]. 2023 [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT03424018.

15. Savarirayan R, Irving M, Bacino CA et al. C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. N Engl J Med 2019; 381(1): 25-35. https://doi.org/10.1056/NEJMoa1813446.

16. BioMarin Pharmaceutical. A Study to Evaluate Long-Term Safety, Tolerability, & Efficacy of BMN 111 in Children With Achondroplasia (ACH) (ACH) [online]. 2023 [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT02724228.

17. BioMarin Pharmaceutical. A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients With Achondroplasia [online]. 2021 [Accessed: 10.01.2024]. URL: https://clinicaltrials.gov/study/NCT01603095.

18. Centers for Disease Control and Prevention. Clinical Growth Charts [online]. [Accessed: 10.08.2021]. URL: https://www.cdc.gov/growthcharts/clinical_charts.htm.

19. Hoover-Fong JE, Alade AY, Hashmi SS et al. Achondroplasia Natural History Study (CLARITY): a multicenter retrospective cohort study of achondroplasia in the United States. Genet Med 2021; 23(8): 1498-1505. https://doi.org/10.1038/s41436-021-01165-2.

20. BioMarin. VOXZOGO 0,4 mg/- 0,56 mg/- 1,2 mg Pulver und Lösungsmittel zur Herstellung einer Injektionslösung [online]. 2023 [Accessed: 09.01.2024]. URL: https://www.fachinfo.de.

21. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. S1-Leitline Kleinwuchs [online]. 2023 [Accessed: 09.01.2024]. URL: https://register.awmf.org/assets/guidelines/174-004l_S1_Kleinwuchs_2023-07.pdf.

22. Cormier-Daire V, AlSayed M, Ben-Omran T et al. The first European consensus on principles of management for achondroplasia. Orphanet J Rare Dis 2021; 16(1): 333. https://doi.org/10.1186/s13023-021-01971-6.

23. Savarirayan R, Ireland P, Irving M et al. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. Nat Rev Endocrinol 2022; 18(3): 173-189. https://doi.org/10.1038/s41574-021-00595-x.

24. Uniform Data System for Medical Rehabilitation. The WeeFIM II Clinical Guide, Version 6.4 [unpublished]. 2016.

25. HealthAct C. H. Q. ITQOL: Infant Toddler Quality of Life Questionnaire [online]. 2021 [Accessed: 30.08.2023]. URL: https://www.healthactchq.com/survey/itqol.

26. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-116.html.