Vosoritide (achondroplasia)

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

EXTRACT

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No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

IQWiG thanks the respondent and the German association of short-statured people and their families (Bundesverband Kleinwüchsiger Menschen und ihre Familien e. V., BKMF) for participating in the written exchange and for their support. The respondent and the BKMF were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

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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
FGFR3	fibroblast growth factor receptor 3
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
HLT	High Level Term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITQOL	Infant Toddler Quality of Life Questionnaire
NFAH	near-final adult height
PedsQL	Pediatric Quality of Life Inventory
QoLISSY	Quality of Life of Short Stature Youth
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 4 September 2023.

Research question

The aim of this report is to assess the added benefit of vosoritide in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with achondroplasia 2 years of age and older whose epiphyses are not closed.

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 with achondroplasia[b] 2 years of age and older whose epiphyses are not closed	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 that 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 presented by the company in the dossier. Randomized controlled trials (RCTs) with a minimum treatment duration of 52 weeks are used for the derivation of the added benefit.

Study pool and study design

The study pool for the benefit assessment comprises the studies BMN 111-206 and BMN 111-301 (hereinafter referred to as "Study 206" and "Study 301"). 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. In addition to the studies mentioned, these contain data from the studies BMN 111-901, BMN 111-202, BMN 111-205, BMN 111-208 and BMN 111-302.

Study 206

Study 206 is a phase 2, double-blind, 52-week RCT evaluating 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.

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 therapeutic indication only includes patients with genetically confirmed achondroplasia 2 years of age and older. Thus, only the analyses of the relevant subpopulation (Cohort 1: age ≥ 2 to < 5 years, 15 patients in the intervention arm and 16 in the comparator arm) are used for the benefit assessment. Cohorts 2 and 3 are therefore no longer considered below. Patients in Cohort 1 received approval-compliant treatment with subcutaneous vosoritide 15 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 is assumed in Study 206.

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 and morbidity.

For easier reading, the relevant subpopulation of Study 206, i.e. Cohort 1 of Study 206, will only be referred to as “Study 206” in the following text.

Study 301

Study 301 is a phase 3, double-blind, 52-week RCT evaluating vosoritide versus placebo in children aged 5 to < 18 years with genetically confirmed achondroplasia.

The study included patients who were active participants in the observational BMN 111-901 study at the time of study entry and who had at least a 6-month period of growth assessments (including height) after participation in the BMN 111-901 study. In addition, the epiphyses were not allowed to be closed and the annual growth velocity had to be ≥ 1.5 cm/year.

In Study 301, a total of 60 patients were randomized to the intervention arm and 61 to the comparator arm.

Treatment with vosoritide was in compliance with the approval. Patients in the comparator arm received subcutaneous injection with placebo once a day. In addition to the study

medication, concomitant treatments were permitted at the discretion of the investigator. Overall, adequate implementation of the ACT BSC is assumed in Study 301.

The primary outcome of Study 301 was the change in annualized growth velocity. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Meta-analytical summary of results

The therapeutic indication for vosoritide includes patients 2 years of age and older whose epiphyses are not closed. The relevant subpopulation of Study 206 comprises children aged between 2 and < 5 years; patients aged 5 to < 18 years were included in Study 301. Apart from age, there are no important differences between the populations of Study 206 and Study 301.

Although there are no overlaps between the age groups of studies 206 and 301, the consideration of the subgroup analyses on the characteristic of age at baseline for the outcome of height (z-score), which is relevant (and age-adjusted) in the present assessment, supports a meta-analytical summary. Furthermore, nothing in the respective study suggests that there is an important effect modification by the characteristic of age at baseline for the outcomes used for the benefit assessment. In the present data situation, it is therefore assumed that a meta-analysis of the studies 206 and 301 is meaningful and feasible. Where possible and meaningful, the results of the outcomes of the relevant studies 206 and 301 used for the benefit assessment are pooled in a meta-analysis.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the studies 206 and 301 was rated as low. The risk of bias was rated as high for the outcomes of functional independence, assessed using the Pediatric Functional Independence Measure II (WeeFIM), and health-related quality of life, assessed using the Pediatric Quality of Life Inventory (PedsQL). The risk of bias for all other outcomes was rated as low.

Because of this, no more than hints, e.g. of an added benefit, can be determined for the outcomes of functional independence (WeeFIM) and health-related quality of life (PedsQL). For outcomes that cannot be pooled in a meta-analysis or for which pooling is not meaningful, at most indications, e.g. of an added benefit, can be determined. For all outcomes for which a meta-analytical summary is possible and meaningful, at most proof, e.g. of an added benefit, can be determined.

Results

Mortality

All-cause mortality

There were no events in the outcome of all-cause mortality. Thus, no significant differences between treatment groups were shown in the studies 206 and 301. 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)

The meta-analysis of the studies 206 and 301 showed a significant difference in favour of vosoritide for the outcome of height (z-score). There is proof of an added benefit of vosoritide + BSC in comparison with BSC. For patients aged ≥ 2 to < 5 years (Study 206), this advantage resulted from an average growth of 6.38 cm under vosoritide treatment, whereas patients in the comparator arm grew 5.41 cm (difference: 0.96 cm). Patients ≥ 5 years of age (Study 301) grew an average of 5.86 cm under vosoritide treatment and 4.29 cm under placebo (difference: 1.57 cm). The supporting analyses of the long-term data on the outcome of height (z-score) show that the effect is sustained, and do not call into question the results of the meta-analysis of the studies 206 and 301 with regard to the benefit of vosoritide.

Functional independence (WeeFIM)

In Study 206, no significant difference between treatment groups was shown for the outcome of functional independence, recorded with the WeeFIM. For Study 301, no suitable data are available. This results in no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Coping and beliefs (QoLISSY)

The outcomes of coping and beliefs (Quality of Life of Short Stature Youth [QoLISSY] were only recorded in Study 301. Suitable data are only available for children ≥ 8 years of age from the patient-reported version. No significant difference between treatment groups was found. This results in 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

QoLISSY and PedsQL

The QoLISSY and PedsQL instruments were recorded exclusively in Study 301. Suitable data are only available for children ≥ 8 years of age from the patient-reported version. There was no significant difference between treatment groups for the outcome of health-related quality of life, recorded using QoLISSY or PedsQL. 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, severe AEs and discontinuation due to AEs

In Study 206, no events occurred in the outcomes of serious adverse events (SAEs) and discontinuation due to adverse events (AEs). In Study 301, there were no significant differences between treatment groups for severe AEs and discontinuation due to AEs. For the outcome of SAEs, the meta-analysis of the studies 206 and 301 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 for these outcomes.

Injection site reactions (AE)

For the outcome of injection site reactions (AE), the meta-analysis of the studies 206 and 301 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.

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

For patients with achondroplasia whose epiphyses are not closed, the meta-analysis of studies 206 and 301 showed a positive effect of vosoritide treatment for the outcome of height (z-score). The supporting consideration of the long-term data from the studies 901/301/302 (2-year comparison with placebo), 206/208 (up to 2.5 years, comparison with baseline), 301/302 (up to 3.5 years, comparison with baseline) and 202/205 (up to 7 years, comparison with baseline) shows that the effect on the outcome of height (z-score) is sustained. No conclusions can be drawn for a longer period than 7 years due to low patient numbers at the later documentation time points. Overall, the long-term data do not call into question the results of the meta-analysis of the studies 206 and 301 with regard to the benefit of vosoritide.

For the outcome of height (z-score), it is difficult to estimate what a specific change in the outcome of height (z-score) means for the individual patient. In addition, no data are yet available on patients who received vosoritide continuously from the age of 2 years until closure of the growth plates. This means that the final height that can ultimately be reached

[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].

with vosoritide treatment is not yet precisely known. For the present benefit assessment, an added benefit in the outcome of height (z-score) can therefore not be quantified.

At outcome level, there is initially proof of an added benefit for height (z-score). Based on the consideration of height (z-score), however, at best an indirect conclusion can be drawn about the effect of vosoritide treatment on the late complications and functional impairments associated with achondroplasia. However, outcomes that directly record late complications or functional impairments were not recorded in the available studies or did not show any statistically significant effects in favour of vosoritide. In addition, no suitable data are available for the other anthropometric outcomes (upper to lower body segment ratio and body proportion ratios of the extremities), which reflect achondroplasia-associated characteristics. Based on the results of the operationalization presented by the company, no change in disproportionate growth was shown, however. This results in limitations in the certainty of conclusions regarding the added benefit of vosoritide compared with the ACT BSC.

In the outcomes for which a meta-analysis of studies 206 and 301 was not possible or meaningful, there were neither positive nor negative effects of treatment with vosoritide at the level of the individual studies.

Due to the limitations described above, no more than an indication of added benefit is determined in the overall assessment.

In summary, there is an indication of a non-quantifiable added benefit of vosoritide compared with the ACT BSC for patients with achondroplasia 2 years of age and older whose epiphyses are not closed.

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] 2 years of age and older whose epiphyses are not closed	BSC[c]	Indication of non-quantifiable added benefit

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 that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
d. No data are available for patients aged ≥ 15 years at the start of treatment.

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

The 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 this report is to assess the added benefit of vosoritide in comparison with BSC as ACT in patients with achondroplasia 2 years of age and older whose epiphyses are not closed.

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 with achondroplasia[b] 2 years of age and older whose epiphyses are not closed	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 that 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 presented by the company in the dossier. RCTs with a minimum treatment duration of 52 weeks were used for the derivation of the added benefit. The company chose no restrictions regarding a minimum treatment duration or the study type for the evidence it used. 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 list on vosoritide (status: 12 July 2023)
- bibliographical literature search on vosoritide (last search on 28 June 2023)
- search in trial registries/trial results databases for studies on vosoritide (last search on 28 June 2023)
- search on the G-BA website for vosoritide (last search on 28 June 2023)

To check the completeness of the study pool:

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

The check did not identify any additional relevant study. Since the present assessment also considered single-arm long-term data as supplementary information, these were also checked for completeness. This check also did not identify any additional relevant study.

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

I 3.1 Studies included

The studies listed in Table 5 were 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)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
BMN 111-206 (206[c])	Yes	Yes	No	Yes [3,4]	Yes [5-7]	No
BMN 111-301 (301[c])	Yes	Yes	No	Yes [8,9]	Yes [10-12]	Yes [13]

a. Study sponsored by the company.
b. References 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.

CSR: clinical study report; RCT: randomized controlled trial

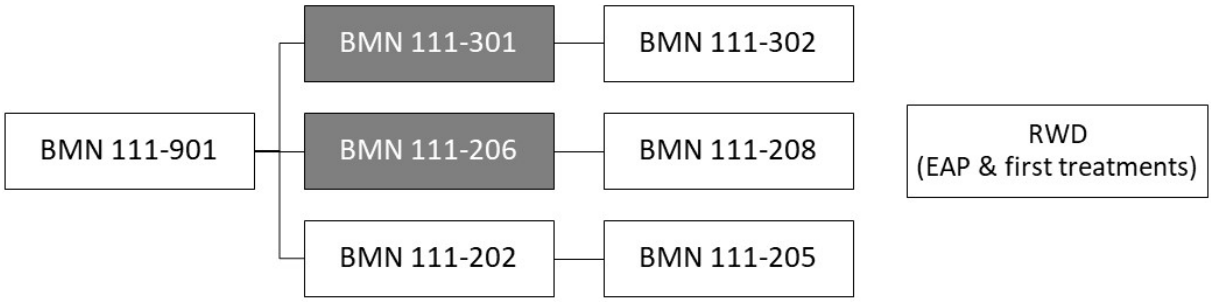
The study pool for the benefit assessment of vosoritide in patients with achondroplasia 2 years of age and older whose epiphyses are not closed consists of the RCTs BMN 111-206 (hereinafter referred to as "Study 206") and BMN 111-301 (hereinafter referred to as "Study 301"). To assess the sustainability of the effects of vosoritide, partial results of the long-term data presented by the company are considered as supplementary information (see following section).

Long-term data

The company presented various analyses to show the long-term effects of treatment with vosoritide. Depending on the analysis, these include results on selected outcomes over the periods of the RCTs and their extension studies (hereinafter referred to as "301/302" and "206/208"), over the period of the BMN 111-202 and BMN 111-205 studies (hereinafter referred to as "202/205"), as well as over the period of the observational BMN 111-901 study of at least 1 year, the RCT BMN 111-301, and the first year of treatment of the BMN 111-302 extension study (hereinafter referred to as "901/301/302").

The following text first describes the studies BMN 111-901, BMN 111-302, BMN 111-208, BMN 111-202 and BMN 111-205 (hereinafter referred to without BMN 111), and then the presented analyses and how they are handled in the present benefit assessment.

Figure 1 presents an overview of the evidence and of the relation between the studies.



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

Figure 1: Presentation of how the studies presented by the company are related

Study characteristics

Study 901

Study 901 [14] is a completed, prospective observational study to collect baseline growth measurements on patients being considered for enrolment in future intervention studies. The study included 363 patients aged 0 to ≤ 17 years with achondroplasia whose epiphyses are not closed. The growth measurements were taken at 3-month intervals from Month 0. For a

transition to a subsequent intervention study (202, 206 or 301), growth data had to be available over a period of at least 6 months, except for children aged 0 to 3 months.

Studies 202 and 205

Study 202 [15] is a completed, sequential, open-label phase 2 dose escalation study to evaluate the safety and tolerability of vosoritide therapy. However, growth parameters such as height z-scores and annualized growth velocity were also recorded as part of the study. The study enrolled patients 5 to ≤ 14 years of age who had participated in Study 901 for at least 6 months (see above). Furthermore, the patients had to meet the additional requirements stipulated in the inclusion and exclusion criteria with regard to concomitant diseases (e.g. absence of autoimmune disorders, inflammatory bowel diseases or defined cardiovascular diseases) or concomitant treatments (e.g. no chronic therapy with antihypertensive medications or growth hormones). In total, 35 patients were enrolled in Study 202 and allocated to the 4 sequential dose cohorts. Cohort 1 (2.5 µg/kg) and Cohort 2 (7.5 µg/kg) each comprised 8 patients. Ten patients were included in Cohort 3 (15 µg/kg), and 9 patients were included in Cohort 4 (30 µg/kg). After an initial treatment phase of 6 months, Cohorts 1 and 2 were increased to a daily dose of 15 µg/kg for the following 18 months, whereas Cohorts 3 and 4 maintained the initial dosage. After completion of the 24-month treatment phase in Study 202, patients could transition to the open-label extension study 205 [16]. A total of 30 patients in the ongoing Study 205 continue their last dose from Study 202 until they reach near-final adult height (NFAH), defined as evidence of growth plate closure and an annualized growth velocity < 1.5 cm per year. Patients are observed until they reach NFAH, but for at least 5 years if NFAH is reached earlier. The company presented analyses of the ongoing Study 205 for the data cut-off of 25 February 2022.

Study 208

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 208 [17] 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 continues until the NFAH is reached (for the definition, see the Section on studies 202 and 205). For the ongoing Study 208, the company presented analyses of the data cut-off of 26 January 2022.

Study 302

Patients who completed the placebo-controlled Study 301 (see Section I 3.2 for a description) then had the opportunity to take part in the open-label, single-arm extension study 302 [18] and continue treatment with vosoritide there. A total of 119 patients were enrolled in Study 302. Patients are observed until they reach NFAH (for the definition, see Section on

studies 202 and 205), but for at least 5 years if NFAH is reached earlier. For the ongoing Study 302, the company presented analyses of the data cut-off of 25 February 2022.

Presented analyses and handling in the benefit assessment

Table 6 shows an overview of the analyses of the long-term data on vosoritide presented by the company.

Table 6: Overview of analyses of long-term data on the outcome of height (z-score)[a] presented by the company (multipage table)

Study **Analyses**	**Age of the patients**	**Comparative [yes/no]**	**Period or point in time[b] (of which informative[c])**	**Supporting consideration [yes/no]**
301/302				
Change from baseline (z-score compared with healthy CDC reference [19])	≥ 5 years	No (descriptive)	3.5–5 years (3.5 years)	Yes
Change from baseline (z-score compared with achondroplasia reference [20])	≥ 5 years	No (descriptive)	3.5–5 years	No
Vosoritide vs. CLARITY; cross section	≥ 5 years	Yes	3 years	No
901/301/302				
Vosoritide vs. observation/placebo	≥ 5 years	Yes	2 years (2 years)	Yes
202/205				
Change from baseline (z-score compared with healthy CDC reference [19])	≥ 5 years	No (descriptive)	7–8 years (7 years)	Yes
Change from baseline (z-score compared with achondroplasia reference [20])	≥ 5 years	No (descriptive)	7–8 years	No
Vosoritide vs. CLARITY; cross section	≥ 5 years	Yes	7 years	No
206/208				
Change from baseline (z-score compared with healthy CDC reference [19])	≥ 2 years[d]	No (descriptive)	3–3.5 years (2.5 years)	Yes
Vosoritide vs. CLARITY; longitudinal section	≥ 2 years	Yes	1, 2, 3 and 4 years	No
Vosoritide vs. CLARITY; cross section	≥ 2 years	Yes	1, 2, 3 and 4 years	No
Vosoritide vs. observation/placebo; longitudinal section (z-score compared with healthy CDC reference [19])	≥ 2 years	Yes	1, 2, 3 and 4 years	No
Vosoritide vs. observation/placebo; longitudinal section (z-score compared with achondroplasia reference [20])	≥ 2 years	Yes	1, 2, 3 and 4 years	No
Vosoritide vs. observation/placebo; cross section (z-score compared with healthy CDC reference [19])	≥ 2 years	Yes	1, 2, 3 and 4 years	No
Vosoritide vs. observation/placebo; cross section (z-score compared with achondroplasia reference [20])	≥ 2 years	Yes	1, 2, 3 and 4 years	No

Table 6: Overview of analyses of long-term data on the outcome of height (z-score)[a] presented by the company (multipage table)

Study Analyses	Age of the patients	Comparative [yes/no]	Period or point in time[b] (of which informative[c])	Supporting consideration [yes/no]
a. For the relevance of the outcome in the present benefit assessment, see Section I 4.1. 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. Descriptive data are also available for patients < 2 years of age. These patients are not covered by the present therapeutic indication, however. CDC: Centers for Disease Control and Prevention				

Descriptive analyses

Analyses 301/302 include descriptive data from earlier vosoritide treatment (children who were in the intervention arm of RCT 301 [vos/vos]) and from delayed vosoritide treatment (children who were in the placebo arm of RCT 301 and then received vosoritide in the extension study [plc/vos]). In addition, the company provided a descriptive presentation of the pooled results of the original vos/vos arm and plc/vos arm. For the supporting consideration of long-term effects, only the vos/vos arm is of interest, as this represents a longer period with administration of vosoritide.

The analyses 206/208 include descriptively reported results separately for the respective age groups of 0 to < 6 months, 6 months to < 24 months, 24 to < 60 months, ≥ 60 months. The results presented in Module 4 A for the individual age cohorts include both the children who were in the intervention arm of RCT 206 and continued to receive vosoritide in the extension study (vos/vos [incl. sentinels; for a description see section on the description of Study 206]) and the children who were in the placebo arm of RCT 206 and received vosoritide in the extension study (plc/vos). Since vosoritide is approved for patients 2 years of age and older, the analyses with children aged 24 to < 60 months and ≥ 60 months, and of these only the vos/vos-arms without sentinels, which represent a longer period with vosoritide treatment, are relevant for the supporting consideration of long-term effects. Analyses excluding the unblinded sentinel patients are not available.

For the analyses on 202/205, the company provided a descriptive presentation of results of the individual dose cohorts and all included children for various outcomes. For the outcome of height (z-score), the company presented an analysis using a 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). The company considered the analysis that included children of all cohorts to derive the added benefit. Only Cohort 3 is of interest for the

supporting consideration of long-term effects, as only in this cohort of Study 202 was vosoritide administered at the approved dosage. In addition, only the results using the CDC reference population are considered as supporting information for the outcome of height (z-score).

Comparative analyses

Analysis 901/301/302 is a comparison of 2 years of vosoritide therapy versus placebo. The comparator arm was generated by including the children in Study 901 for whom growth measurements were available for at least 1 year and who later transferred to the placebo arm of RCT 301. The intervention arm includes children with 1-year data in extension study 302 who were previously treated with vosoritide in RCT 301. With the same observation period, patients in the intervention arm are therefore 1 year older than those in the comparator arm. This systematic age difference is not relevant for the supporting observation of long-term data of the outcome of height (z-score) due to the age adjustment associated with the z-score. The company did not present a corresponding comparison including studies 206 and 208.

In addition, the company presented cross-sectional analyses of patients treated with vosoritide from studies 301/302 (at year 3), 202/205 (at year 7) and 206/208 (at years 1, 2, 3, 4) in comparison with external control groups of untreated patients with achondroplasia exclusively for the outcome of height (z-score). The company also presented corresponding longitudinal analyses after years 1, 2, 3 and 4 for Study 206/208. The 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 history of achondroplasia patients [20]. In addition, for the analysis 206/208, the company presented a comparison with combined prospective observational data from Study 901, pretreatment data from Study 206 and data from the placebo arms of studies 301 and 206 (901/206/301). For the longitudinal analyses against data from the CLARITY study, matching was performed by gender, 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 (901/206/301), 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 (901/206/301), matching was performed separately for baseline and years 1, 2, 3 and 4 according to age (actual age in months with 1 decimal place ± 1 month) and sex.

The presented cross-sectional analyses versus external control arms are not suitable for the supporting analysis 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 comparison populations. In addition, in the comparison of 206/208 versus CLARITY or 901/206/301 and 301/302 versus

CLARITY, all children from Study 206 or 301 are included in the intervention arm 206/208 or 301/302, i.e. also those who were treated with placebo in Study 206 or 301, as well as the sentinel patients who received unblinded vosoritide in the analysis of 206/208 (see also section on the description of Study 206). Notwithstanding the aforementioned points of criticism , the company did 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 following analyses are considered to support the assessment of the added benefit in order to be able to assess the sustainability of the treatment effects from the RCTs (see Section I 5.2):

1) Descriptive analyses of the changes from baseline:
   - 206/208 (only children who were in the intervention arm of Study 206 and continued treatment with vosoritide in Study 208 [see Figure 24, Figure 28 and Figure 31 of the full dossier assessment])
   - 301/302 (only children who were in the intervention arm of Study 301 and continued treatment with vosoritide in Study 302 [see Figure 22, Figure 25, Figure 29, as well as Figure 32 to Figure 35 of the full dossier assessment])
   - 202/205 (only Cohort 3 [see Figure 23, Figure 27 and Figure 30 of the full dossier assessment])
2) 2-year comparison of vosoritide treatment versus placebo from studies 901/301/302 (see Figure 26 of the full dossier assessment)

For this purpose, only the analyses for the outcomes which showed effects on the basis of the meta-analysis of RCTs 206 and 301 are considered as supportive information. In addition, various outcomes on the relationship between body proportion measurements and annualized growth velocity are presented. If available, figures on time courses in the long-term studies are presented as supplementary information in I Appendix F of the full dossier assessment.

I 3.2 Study characteristics

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

Table 7: Characteristics of the studies included – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

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 (children aged ≥ 24 to < 60 months): ▪ vosoritide (n = 15[c]) ▪ placebo (n = 16) Cohort 2 (children aged ≥ 6 to < 24 months): ▪ vosoritide (n = 8[c]) ▪ placebo (n = 8) Cohort 3 (children aged 0 to < 6 months): ▪ vosoritide (n = 9[c]) ▪ placebo (n = 8) Relevant subpopulation thereof: <u>Cohort 1</u>	Screening: 4 weeks Treatment: 52 weeks Observation: 4 weeks[d]	16 centres in Australia, Japan, United Kingdom, United States 6/2018–1/2022	Primary: body length/height[e] based on z-scores, as well as safety and tolerability Secondary: mortality, morbidity, health status
301[f]	RCT, double-blind, parallel	Children with genetically confirmed achondroplasia aged 5 to < 18 years[g]	vosoritide (N = 60) placebo (N = 61)	Screening: 4 weeks Treatment: 52 weeks Observation: 4 weeks[h]	24 centres in Australia, Germany, Japan, Spain, Turkey, United Kingdom, United States 11/2016–10/2019	Primary: change from baseline in annualized growth velocity at 52 weeks Secondary: mortality, morbidity, health-related quality of life, AEs

Table 7: Characteristics of the studies included – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. In order to participate in Study 206, patients in Cohort 1 had to have previously participated in the observational BMN 111 901 study for ≥ 6 months to collect growth data. 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. Sentinel patients received open-label vosoritide and were monitored for 12 weeks (Cohort 1) or 8 days (Cohorts 2 and 3) to assess short-term safety and pharmacokinetics. Only after approval by the data monitoring committee were the remaining patients included in the respective cohort. Cohorts 1 and 2 each included 4 sentinels, and Cohort 3 included 3 sentinels.
d. The safety follow-up visit was not conducted if the patient transitioned to another vosoritide study or registry within 4 weeks of the last dose.
e. Length was obtained in a supine position; height was measured standing up.
f. In order to participate in Study 301, patients had to have previously participated in the observational BMN 111-901 study for ≥ 6 months to collect growth data. Following Study BMN 111-301, all eligible patients could continue treatment with vosoritide in the open-label extension study BMN 111-302. A total of 119 patients transitioned to the open-label extension study.
g. Originally, an upper age limit of < 15 years was planned for recruitment. With Protocol Amendment 2 dated 27 April 2017, the upper age limit for recruitment was extended to < 18 years.
h. With Amendment 4 to the study protocol dated 1 February 2019, the observation period was extended from 2 weeks to 4 weeks. The safety follow-up visit was not conducted if the patient transitioned to Study BMN 111-302 within 2 or 4 weeks of the last dose.

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

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

Study	Intervention	Comparison
206	Vosoritide SC 15 µg/kg body weight, 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[a], 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 months ▪ chronic therapy with antihypertensive medications[b], 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) **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	
301	Vosoritide SC 15 µg/kg body weight, once daily	Placebo SC, once daily
	Disallowed pretreatment ▪ growth hormones, insulin-like growth factor 1, or anabolic steroids in the previous 6 months or for longer than 6 months ▪ hip surgery atypical for achondroplasia patients ▪ limb-lengthening surgery ≤ 18 months, or surgery involving disruption of bone cortex (except tooth extraction) ≤ 6 months prior to screening and without completed healing without sequelae ▪ current chronic therapy with antihypertensive medications[b], GnRH agonists, medications that may impair or enhance compensatory tachycardia, diuretics, or other drugs that may alter renal or tubular function ▪ new initiation of sleep apnoea treatment < 2 months prior to screening ▪ corticosteroids for ≥ 1 month in the previous 12 months ▪ other investigational products or investigational medical devices (< 6 months prior to screening) for achondroplasia or short stature (at any time) **Allowed pretreatment** ▪ low-dose inhaled steroid for asthma, or intranasal steroids **Disallowed concomitant treatment** ▪ planned limb-lengthening surgery, or surgery involving disruption of bone cortex (except tooth extraction) **Allowed concomitant treatment** ▪ additional drugs at the investigator's discretion	

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

Study	Intervention	Comparison
a. From Protocol Amendment 1 (16 August 2018), patients with previous cervicomedullary decompression could participate after consultation with the clinical monitor. b. Includes ACE inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium channel blockers, cardiac glycosides, and systemic anticholinergic agents. ACE: angiotensin converting enzyme; ALT: alanine aminotransferase; AST: aspartate aminotransferase; 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

Study 206 is a phase 2, double-blind, 52-week RCT evaluating 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. Furthermore, no evidence 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, 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.

At the beginning of the study, 4 sentinel patients in the oldest cohort (Cohort 1) were initially treated with open-label vosoritide to evaluate 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, and the procedure was similar. Four sentinel patients in Cohort 2, and 3 sentinel patients in Cohort 3 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 within Cohorts 1 and 2 according to the characteristic of age (≥ 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 randomization, patients in Cohort 1 received approval-compliant treatment with subcutaneous vosoritide 15 µg/kg once daily [21] or with subcutaneous placebo once daily. For patients in Cohort 2, the vosoritide dose was increased from 15 µg/kg to 30 µg/kg after analysis of the pharmacokinetic data. The initial dose in Cohort 3 was 30 µg/kg. 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 and morbidity. 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

Study 206 included patients aged 0 to < 5 years. However, the present therapeutic indication only includes patients with genetically confirmed achondroplasia 2 years of age and older. Thus, only the analyses of the relevant subpopulation (Cohort 1: age ≥ 2 to < 5 years, without sentinel patients), which included 15 patients in the intervention arm and 16 in the comparator arm, are used for the benefit assessment.

For easier reading, the relevant subpopulation of Study 206, i.e. Cohort 1 of Study 206, will only be referred to as “Study 206” in the following text.

Study 301

Study 301 is a phase 3, double-blind, 52-week RCT evaluating vosoritide versus placebo in children aged 5 to < 18 years with genetically confirmed achondroplasia. Only patients up to 14.9 years of age were actually enrolled.

The study included patients who were active participants in the observational BMN 111-901 study at the time of study entry and who had at least a 6-month period of growth assessments (including height) after participation in the BMN 111-901 study. In addition, the epiphyses were not allowed to be closed and the annual growth velocity had to be ≥ 1.5 cm/year. Planned or expected limb-lengthening surgery or bone-related surgery during the study period, fracture of the long bones or spine within 6 months prior to screening, hip surgery or hip dysplasia atypical for achondroplasia patients, and severe untreated sleep apnoea led to exclusion from the study.

Randomization was carried out in a 1:1 ratio and was stratified by the characteristics of sex (male versus female) and Tanner stage (stage I versus stage > I). In Study 301, a total of 60 patients were randomized to the intervention arm and 61 to the comparator arm.

Treatment with vosoritide was in compliance with the approval [21]. Patients in the comparator arm received subcutaneous injection with placebo once a day. 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 301 was the change in annualized growth velocity. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects. Following Study 301, all patients had the option to continue treatment with vosoritide in the open-label extension study BMN 111-302.

Implementation of the appropriate comparator therapy 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 [22]. There are also European and international consensus statements on achondroplasia [23,24].

In general, patients with achondroplasia may have various complications, including in particular restrictive pulmonary disease, infections, sleep apnoea, otitis media, cervicomedullary compression, musculoskeletal manifestations (e.g. bow legs) leading to chronic pain, and cardiovascular disorders [24]. Accordingly, a BSC includes appropriate therapies to treat possible complications (drugs, any necessary surgery, physiotherapy). In addition, the shorter stature and the different proportions of the body compared with normal body growth result in a need for aids to improve aspects of daily living [23]. The current general German S1 guideline on short stature also points out that paediatric psychological co-management may be useful [22].

According to the inclusion and exclusion criteria in the studies 206 and 301, children with planned spinal surgery, limb-lengthening surgery, or surgery for cervicomedullary compression (Study 206 only) during the study period were excluded from participation in the study. In addition, patients were not allowed to have severe untreated sleep apnoea at the time of the screening. However, this does not rule out the possibility that appropriate treatment was initiated or carried out during the study period if necessary.

In studies 206 and 301, the use of drugs was generally permitted during the study period. For example, 63% of children in Cohort 1 received analgesics in the comparator arm of Study 206 during the study period, compared with 39% in Study 301. The administration of systemic

antibiotics was also initiated in 56% (Study 206) and 33% (Study 301) of patients. There were only restrictions with regard to a few medications and therapies, including antihypertensive medications or the disallowed use of gonadotropin-releasing hormone (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, this did not apply to any patient in either study. GnRH agonists are not approved for the treatment of achondroplasia in Germany and are also not mentioned in the German S1 guideline [22]. Since growth hormones are not a useful therapeutic approach for genetic achondroplasia, prohibiting these drugs is not a relevant restriction of the ACT. Similarly, 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 considered to be adequately implemented overall.

Characteristics of the study populations

Table 9 shows the characteristics of the patients in the studies included.

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

Study	Study 206		Study 301	
Characteristic Category	Vosoritide + BSC	Placebo + BSC	Vosoritide + BSC	Placebo + BSC
	N[a] = 15	N[a] = 16	N[a] = 60	N[a] = 61
Age [years], mean (SD)	3.2 (0.8)	3.6 (1.0)	8.4 (2.4)	9.1 (2.5)
Sex [F/M], %	53/47	56/44	48/52	46/54
Tanner stage, n (%)				
I	Not recorded[b]		48 (80)	48 (79)
> I	Not recorded[b]		12 (20)	13 (21)
Family origin, n (%)				
White	8 (53)	13 (81)	45 (75)	41 (67)
Asian	6 (40)	3 (19)	10 (17)	13 (21)
Multiple	1 (7)	0 (0)	2 (3)	5 (8)
Black or African American	0 (0)	0 (0)	3 (5)	2 (3)
Height (z-score)[c], mean (SD)	−4.3 (0.8)	−5.1 (1.2)	−5.1 (1.1)	−5.1 (1.1)
Height [cm], mean (SD)	79.8 (4.9)	79.4 (6.8)	100.2 (11.9)	102.9 (11.0)
Annualized growth velocity [cm/year], mean (SD)	4.7 (1.7)	4.2 (1.8)	4.3 (1.5)	4.1 (1.2)
Upper to lower body segment ratio, mean (SD)	2.4 (0.2)	2.3 (0.2)	2.0 (0.2)	2.0 (0.2)
Arm span to standing height ratio, mean (SD)	0.9 (0.1)	0.9 (0.0)	0.9 (0.1)	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)	1.1 (0.1)
Upper leg length to knee to heel length ratio, mean (SD)	0.6 (0.1)	0.6 (0.1)	0.7 (0.1)	0.7 (0.1)
Upper leg length to tibial length ratio, mean (SD)	1.0 (0.2)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)
Treatment discontinuation, n (%)	0 (0)	0 (0)	2 (3)	0 (0)
Study discontinuation, n (%)	0 (0)	0 (0)	2 (3)	0 (0)

a. Number of randomized patients (for Study 206, this corresponds to the relevant subpopulation). Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. The Tanner stage was not recorded in Study 206, but all patients included were in Tanner stage I due to their age.
c. Age- and sex-adjusted numbers of standard deviations (z-scores) were determined against a US reference population of average stature.

AE: adverse event; BSC: best supportive care; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics within Study 206 and Study 301 are sufficiently balanced between the intervention and the comparator arms. In the treatment arms of both studies, the majority

of patients were of white (53 to 81%) or Asian family origin (17 to 40%), but the proportion of children of white and Asian family origin differed notably between the arms within Study 206. Study 206 enrolled more girls (53% to 56%), while Study 301 enrolled more boys (53%). The mean age in Study 206 was 3.2 years in the intervention arm and 3.6 years in the comparator arm. In Study 301, which included older patients, the mean age was 8.4 years in the treatment arm and 9.1 years in the comparator arm. Although patients up to the age of < 18 years could participate in Study 301 per inclusion criterion, the maximum age was 13.1 years in the intervention arm and 14.9 years in the comparator arm.

In Study 206, the deviation in patient height compared with the US reference population was smaller in the intervention arm (z-score: −4.3) than in the comparator arm (z-score: −5.1). The height z-score in both treatment arms of Study 301 was −5.1 the start of treatment. The body proportion ratios were largely balanced in both studies. With regard to the upper to lower body segment ratio, the younger patients in Study 206 showed higher disproportionality with values of 2.3 to 2.4 compared with the patients in Study 301 (mean 2.0).

There were no treatment or study discontinuations in Study 206. In the intervention arm of Study 301, 2 patients discontinued treatment and 2 patients discontinued the study.

Meta-analytical summary of results

The therapeutic indication for vosoritide includes patients 2 years of age and older whose epiphyses are not closed [21]. The relevant subpopulation of Study 206 comprises children aged between 2 and < 5 years; patients aged 5 to < 18 years were included in Study 301. Apart from age, there are no important differences between the populations of Study 206 and Study 301. In principle, a meta-analytical summary of the results of the 2 studies is therefore conceivable.

Although there are no overlaps between the age groups of studies 206 and 301, the consideration of the subgroup analyses on the characteristic of age at baseline for the outcome of height (z-score), which is relevant (and age-adjusted) in the present assessment, supports a meta-analytical summary (see also Figure 6 in the full dossier assessment). Furthermore, nothing in the respective study suggests that there is an important effect modification by the characteristic of age at baseline for the outcomes used for the benefit assessment. There is a statistically significant interaction (p = 0.0310) between treatment and the characteristic of age at baseline in Study 301 only for the outcome of annualized growth velocity presented as supplementary information. Thus, the observed advantage of vosoritide in annualized growth velocity is no longer statistically significant in the oldest subgroup (11 to < 15 years). Nevertheless, the effect in this age group also points in the same direction. Overall, it is therefore assumed that there is no relevant effect modification by age at baseline, even beyond the cut-off value of 5 years. In the present data situation, it is therefore assumed

that a meta-analysis of the studies 206 and 301 is meaningful and feasible. Where possible and meaningful, the results of the outcomes of the relevant studies 206 and 301 used for the benefit assessment are pooled in a meta-analysis. Outcomes presented as supplementary information are also pooled in a meta-analysis. Forest plot of the meta-analyses are presented in I Appendix D of the full dossier assessment.

The company interpreted the results of the studies, which included different age groups of patients with achondroplasia (Study 206: 2 to < 5 years, Study 301: 5 to < 18 years), in a qualitative summary. It justified this with the fact that only one RCT is available for each age group and a meta-analysis can therefore not be carried out.

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
301	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 both studies.

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 Study 301 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)
  - coping and beliefs (QoLISSY)
- Health-related quality of life
  - PedsQL
  - QoLISSY
- 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 made by the company, which used further outcomes in the dossier (Module 4 A).

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

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)	Coping and beliefs (QoLISSY[c])	Health-related quality of life (QoLISSY[d])	Health-related quality of life (PedsQL)	SAEs	Severe AEs[e]	Discontinuation due to AEs	Injection site reactions (HLT, AEs)	Other specific AEs
206	Yes	Yes	No[f]	No[f]	Yes	No[g]	No[g]	No[g]	Yes[h]	Yes[h]	Yes	Yes	No[i]
301	Yes	Yes	No[f]	No[f]	No[f]	Yes[j]	Yes[j]	Yes[j]	Yes[h]	Yes[h]	Yes	Yes	No[i]

a. Deaths were recorded as part of the 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. Includes the domains of coping and beliefs.
d. Includes the physical, social and emotional domains and the total score calculated from these.
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. No suitable data available, see body of text below.
g. Outcome not recorded.
h. Includes potentially 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. No other specific AEs were identified based on the AEs occurring in the relevant studies.
j. Suitable data are only available for patients aged ≥ 8 years from the patient-reported version, see body of text below.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; HLT: High Level Term; PedsQL: Pediatric Quality of Life Inventory; QoLISSY: Quality of Life of Short Stature Youth; 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.

Study 206 and Study 301 used a US reference population according to the CDC [19]. In addition to the results derived from the CDC population as a reference, the company also presented a post-hoc analysis based on a German reference population exclusively for Study 301 [25]. For

subjects aged 24 months or older whose standing height could not be measured, a derived standing height was used by subtracting 0.8 cm from the body length.

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 (see Section I 5.2).

In principle, the German reference population is more relevant for the German health care context and therefore preferable to the US reference population. However, as studies 206 and 301 are pooled in a meta-analysis (see Section I 3.2), and results based on the German reference population are only available for Study 301, the results based on the US reference population are used in the present benefit assessment. Due to only minor differences in the results of the German and US reference populations in Study 301, it is assumed that these results are transferable to the German health care context (see Table 14).

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 901 show that patients in the RCTs 206 and 301 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 disproportionality 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.1 of the full dossier assessment, however. The analyses of the company do not suggest a relevant change in disproportionality from vosoritide therapy.

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 all instruments it used (WeeFIM, ITQOL, QoLISSY and PedsQL). 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, QoLISSY and PedsQL 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 [26]. The instrument queries the current point in time. In the 2 studies 206 and 301, the company recorded the WeeFIM at screening, at Week 26 and at week 52. In Study 206, the WeeFIM was also recorded in the event of premature study discontinuation.

The relevant subpopulation of Study 206 included patients aged 2 to < 5 years, who are comprised by the validation of the WeeFIM. For this study, the WeeFIM is used for the assessment of the added benefit. Study 301 included patients aged 5 to < 18 years with a mean age of 8.4 years in the intervention arm and 9.1 years in the comparator arm. As the validity of the instrument has only been confirmed for children up to the age of 7 years, it is unclear for the majority of patients in Study 301 whether the instrument provides valid results for patients aged > 7 years. For the age group of 5 to 7 years, an analysis of the WeeFIM would be possible in principle. However, the company did not present separate analyses for patients aged ≤ 7 years. Hence, no suitable data are available for Study 301.

Health-related quality of life (QoLISSY and PedsQL)

In addition to the generic PedsQL instrument, the company presented QoLISSY, a disease-specific instrument for recording quality of life of children and adolescents with short stature,

for recording health-related quality of life in Study 301. The outcome was recorded at screening, at Week 26 and at Week 52.

With versions for children aged 8 to 12 years and adolescents aged 13 to 18 years, the QoLISSY can be reported by the children and adolescents themselves. There is also a version for parent-reported recording in children and adolescents aged 4 to 18 years. The patient-reported versions consist of 6 domains with 48 items, which are recorded using a 5-point Likert scale. The 3 core domains (physical [6 items], social [8 items] and emotional [8 items]) and the resulting total score are assigned to health-related quality of life. The other domains (coping [10 items], beliefs [4 items] and treatment [14 items]) are predictors of health-related quality of life and are categorized as morbidity. In agreement with the company, the treatment domain is not presented and not considered in the benefit assessment because this domain is only completed for hormone treatment. The parent-reported version of the QoLISSY records an additional 5 items on future and 11 items on the effect on parents. The raw scores of the domains are each transformed onto a scale from 0 to 100, with higher scores indicating better health-related quality of life or lower morbidity. The QoLISSY queries the quality of life within the past 7 days [27].

The company presented analyses of the patient-reported version for patients aged 8 to < 18 years, and analyses of the parent-reported version for patients aged 5 to < 18 years. A direct, patient-reported evaluation of the patients' health-related quality of life using the patient-reported versions of the instruments is favoured over the parent-reported evaluation and is used to assess the added benefit. As health-related quality of life in patients aged 8 to < 18 years is adequately represented by the patient-reported recording, the analyses of the parent-reported versions of the instrument are not used for this age group. The company did not present separate analyses of the parent-reported version for the age group of 5 to < 8 years, for which no patient-reported version was used in Study 301. There is therefore no suitable data available for the age group of 5 to < 8 years. The same situation applies to the recorded PedsQL.

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 only in Study 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 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 [28].

The company assigned the ITQOL to health-related quality of life. However, it did not provide any details on the version of the instrument used. The content validity of the ITQOL could also

not be assessed on the basis of the references provided by the company and other sources. The ITQOL is therefore not used for assessing the added benefit of vosoritide in the present therapeutic indication.

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)	Functional independence (WeeFIM)	Coping and beliefs (QoLISSY[b])	Health-related quality of life (QoLISSY[c])	Health-related quality of life (PedsQL)	SAEs	Severe AEs[d]	Discontinuation due to AEs	Injection site reactions (HLT, AEs)	Other specific AEs
206	L	L	L	H[e]	–[f]	–[f]	–[f]	L[g]	L[g]	L	L	–
301	L	L	L	–[h]	L[i]	L[i]	H[i, j]	L[g]	L[g]	L	L	–

a. Deaths were recorded as part of the AEs.
b. Includes the domains of coping and beliefs.
c. Includes the physical, social and emotional domains and the total score calculated from these.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
f. Outcome not recorded.
g. Includes potentially 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.
h. No suitable data available (see Section I 4.1).
i. Suitable data are only available for patients aged ≥ 8 years from the patient-reported version, see Section I 4.1.
j. Large proportion (> 10%) of patients not considered in the analysis.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; H: high; HLT: High Level Term; L: low; PedsQL: Pediatric Quality of Life Inventory; QoLISSY: Quality of Life of Short Stature Youth; RCT: randomized controlled trial; SAE: serious adverse event; WeeFIM: Pediatric Functional Independence Measure II

The results for the outcome of functional independence, recorded using WeeFIM, have a high risk of bias due to large differences between the treatment groups (> 5 percentage points) with regard to the proportion of patients who were not considered in the analysis. Results for the outcome of health-related quality of life, recorded using PedsQL, have a high risk of bias due to a large proportion (> 10%) of patients not considered in the analysis. The risk of bias for all other outcomes was rated as low.

Because of the high risk of bias, at most hints, e.g. of an added benefit, can be derived on the basis of the available information for the outcomes of functional independence (WeeFIM) and health-related quality of life (PedsQL).

For outcomes that cannot be pooled in a meta-analysis or for which pooling is not meaningful, at most indications, e.g. of an added benefit, can be determined. For all outcomes for which a meta-analytical summary is possible and meaningful, at most proof, e.g. of an added benefit, can be determined.

I 4.3 Results

Table 13 and Table 14 summarize the results from the comparison of vosoritide versus placebo in patients with achondroplasia 2 years of age and older whose epiphyses are not closed.

If possible and meaningful, the present benefit assessment uses the results of studies 206 and 301 pooled in a meta-analysis (see Section I 3.2 for reasons). Forest plots of the meta-analyses calculated by the Institute can be found in I Appendix D of the full dossier assessment. Where necessary, calculations conducted by the Institute 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, dichotomous) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC

Outcome category Outcome Study	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]
Mortality					
All-cause mortality[c]					
206	15	0 (0)	16	0 (0)	–
301	60	0 (0)	61	0 (0)	–
Side effects					
AEs (supplementary information)[d]					
206	15	15 (100.0)	16	16 (100.0)	–
301	60	59 (98.3)	61	60 (98.4)	–
SAEs[d]					
206	15	1 (6.7)	16	1 (6.3)	1.07 [0.07; 15.57]; > 0.999
301	60	3 (5.0)	61	4 (6.6)	0.76 [0.18; 3.26]; 0.802
Total					0.82 [0.23; 2.94]; 0.763[e]
Severe AEs[d, f]					
206	15	0 (0)	16	0 (0)	–
301	60	3 (5.0)	61	3 (4.9)	1.02 [0.21; 4.84]; > 0.999
Discontinuation due to AEs					
206	15	0 (0)	16	0 (0)	–
301	60	1 (1.7)	61	0 (0)	3.05 [0.13; 73.40]; 0.367
Injection site reactions (AEs)					
206	15	12 (80.0)	16	7 (43.8)	1.83 [0.99; 3.37]; 0.042
301	60	51 (85.0)	61	50 (82.0)	1.04 [0.88; 1.22]; 0.710
Total					1.13 [0.96; 1.33]; 0.135[e]

a. Number of patients taken into account in the analysis for calculating the effect estimation (for Study 206, this concurs with the relevant subpopulation); 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 [29]). 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.

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 and health-related quality of life, continuous) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

Outcome category Outcome Study	Vosoritide + BSC N[a]	Values at baseline mean (SD)	Change at Week 52 LS mean [95% CI]	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at Week 52 LS mean [95% CI]	Vosoritide + BSC vs. placebo + BSC MD [95% CI]; p-value
Morbidity							
Height (z-score)							
206[b]	15	−4.27 (0.81)	0.27 [0.04; 0.50]	16	−5.13 (1.15)	−0.06 [−0.28; 0.16]	0.33 [0.00; 0.67]; 0.051[c]
301							
US reference population[b]	60	−5.13 (1.11)	0.27 [0.18; 0.36]	61	−5.14 (1.07)	−0.01 [−0.10; 0.09]	0.28 [0.17; 0.39]; < 0.001[d]
German reference population (supplementary information)[e]	*60*	*−5.69 (1.11)*	*0.28 [0.20; 0.35]*	*61*	*−5.68 (1.09)*	*−0.01 [−0.09, 0.07]*	*0.28 [0.19, 0.37]; < 0.001[d] SMD [95% CI] ND*
Total							0.28 [0.18; 0.39]; < 0.001[f]
Annualized growth velocity [cm/year], (supplementary information)							
206	*15*	*4.74 (1.68)*	*1.99 [1.31; 2.67]*	*16*	*4.20 (1.78)*	*0.89 [0.23; 1.55]*	*1.10 [0.13; 2.07]; 0.028[g]*
301	*60*	*4.26 (1.53)*	*1.71 [1.40; 2.01]*	*61*	*4.06 (1.20)*	*0.13 [−0.18; 0.45]*	*1.57 [1.22; 1.93]; < 0.001[d]*
Total							*1.51 [1.18; 1.85]; < 0.001[f]*
Functional independence (WeeFIM)[h]							
Total score							
206	15	63.7 (29.5)	12.3 (18.1)[i]	14	74.8 (20.4)	11.2 (11.1)[i]	1.1 [−10.44; 12.64]; 0.846[j]
301	No suitable data[k]						
Self-care							
206	15	22.3 (13.2)	5.8 (7.6)[i]	14	27.1 (10.6)	6.4 (6.0)[i]	−0.6 [−5.84; 4.64]; 0.816[j]
301	No suitable data[k]						
Mobility							
206	15	19.0 (8.9)	3.9 (5.8)[i]	14	22.8 (6.4)	2.2 (3.4)[i]	1.7 [−1.96; 5.36]; 0.349[j]
301	No suitable data[k]						
Cognition							
206	15	22.5 (10.4)	2.6 (5.8)[i]	14	24.9 (7.2)	2.6 (4.0)[i]	0.0 [−3.82; 3.82]; > 0.999[j]

Table 14: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

Outcome category Outcome Study	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
301	No suitable data[k]						
Coping and beliefs (QoLISSY [parent-reported])[l]							
206	Outcome not recorded						
301	No suitable data[m]						
Coping and beliefs (QoLISSY [patient-reported])[l, n]							
Coping							
206	Outcome not recorded						
301	27	50.75 (23.65)	−1.92 (21.54)[i]	36	47.91 (20.49)	−2.26 (23.54)[i]	0.34 [−11.22; 11.90]; 0.953[j]
Beliefs							
206	Outcome not recorded						
301	27	58.33 (28.06)	5.79 (26.74)[i]	33	62.31 (26.81)	−2.65 (25.63)[i]	8.44 [−5.13; 22.01]; 0.218[j]
Health-related quality of life							
QoLISSY (parent-reported)[l]							
206	Outcome not recorded						
301	No suitable data[m]						
QoLISSY (patient-reported)[l, n]							
Total score							
206	Outcome not recorded						
301	26	64.59 (17.57)	4.34 (14.42)[i]	35	66.40 (16.05)	−0.88 (19.02)[i]	5.22 [−3.70; 14.14]; 0.246[j]
Physical							
206	Outcome not recorded						
301	27	56.36 (20.27)	6.73 (17.50)[i]	37	60.95 (17.51)	−0.13 (21.10)[i]	6.86 [−3.09; 16.81][o]
Social							
206	Outcome not recorded						
301	26	66.06 (19.92)	2.44 (15.68)[i]	37	68.02 (20.51)	−2.14 (24.62)[i]	4.58 [−6.38; 15.54][o]
Emotional							
206	Outcome not recorded						
301	27	71.36 (21.59)	2.65 (19.77)[i]	35	70.23 (18.15)	0.80 (21.31)[i]	1.85 [−8.73; 12.43][o]

Table 14: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

Outcome category Outcome Study	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
PedsQL (parent-reported)[l]							
206	Outcome not recorded						
301	No suitable data[m]						
PedsQL (patient-reported)[l, n]							
Total score							
206	Outcome not recorded						
301	25	74.07 (11.87)	0.85 (13.80)[i]	33	75.32 (14.98)	−2.62 (15.06)[i]	3.47 [−4.25; 11.19]; 0.372[j]
Physical functioning							
206	Outcome not recorded						
301	25	77.37 (14.11)	−0.24 (14.04)[i]	33	77.03 (17.72)	−2.02 (16.27)[i]	1.78 [−6.38; 9.94][o]
Emotional functioning							
206	Outcome not recorded						
301	24	75.18 (16.47)	1.88 (17.68)[i]	33	76.29 (18.36)	0.11 (19.50)[i]	1.77 [−8.32; 11.86][o]
Social functioning							
206	Outcome not recorded						
301	25	73.39 (19.72)	−0.20 (25.68)[i]	33	71.14 (19.52)	−5.61 (23.48)[i]	5.41 [−7.58; 18.40][o]
School functioning							
206	Outcome not recorded						
301	25	68.39 (18.56)	2.40 (17.80)[i]	33	75.93 (16.93)	−3.41 (18.97)[i]	5.81 [−4.00; 15.62][o]

Table 14: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: vosoritide + BSC vs. placebo + BSC (multipage table)

Outcome category Outcome Study	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

a. Number of patients taken into account in the analysis for calculating the effect estimation (for Study 206, this concurs with the relevant subpopulation); baseline values may rest on different patient numbers.
b. Analysis based on the US reference population of the CDC with average stature [19].
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. LS means and difference in LS means from ANCOVA with the covariables of treatment, stratum based on sex and Tanner stage, baseline age, baseline AGV, and baseline height z-score. For 2 children in the intervention arm, the values at Week 52 were imputed taking into account the annualized growth velocity at baseline and the last available height measurement.
e. Post hoc analysis based on the growth data from Germany on average height published by the Robert Koch Institute [25].
f. Institute's calculation; meta-analysis with fixed effect (method with inverse variance).
g. LS means and difference in LS means from ANCOVA with the covariables of treatment, sex, age stratum, baseline age, and baseline AGV.
h. 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).
i. Mean (SD).
j. Effect, CI and p-value: Institute's calculation (t-test).
k. The WeeFIM instrument is not sufficiently validated for patients > 7 years of age. The company did not present separate analyses for patients aged 5 to ≤ 7 years (see Section I 4.1).
l. Higher (increasing) values indicate lower morbidity/better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
m. For patients ≥ 8 years of age, health-related quality of life (PedsQL, QoLISSY), and coping and beliefs (QoLISSY) are directly represented via the patient-reported versions of QoLISSY and PedsQL. No separate analyses are available for the parent-reported version for patients < 8 years of age.
n. Includes patients aged ≥ 8 years.
o. Institute's calculation.

AGV: average growth velocity; ANCOVA: analysis of covariance; BSC: best supportive care; CDC: Centers for Disease Control and Prevention; CI: confidence interval; LS: least squares; MD: mean difference; N: number of analysed patients; ND: no data; PedsQL: Pediatric Quality of Life Inventory; QoLISSY: Quality of Life of Short Stature Youth; RCT: randomized controlled trial; SD: standard deviation; WeeFIM: Pediatric Functional Independence Measure II

Mortality

All-cause mortality

There were no events in the outcome of all-cause mortality. Thus, no significant differences between treatment groups were shown in the studies 206 and 301. 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)

The meta-analysis of the studies 206 and 301 showed a significant difference in favour of vosoritide for the outcome of height (z-score). There is proof of an added benefit of vosoritide + BSC in comparison with BSC. For patients aged ≥ 2 to < 5 years (Study 206), this advantage resulted from an average growth of 6.38 cm under vosoritide treatment, whereas patients in the comparator arm grew 5.41 cm (difference: 0.96 cm). Patients ≥ 5 years of age (Study 301) grew an average of 5.86 cm under vosoritide treatment and 4.29 cm under placebo (difference: 1.57 cm). The supporting analyses of the long-term data on the outcome of height (z-score) show that the effect is sustained, and do not call into question the results of the meta-analysis of the studies 206 and 301 with regard to the benefit of vosoritide. A presentation of the supporting long-term data considered can be found in I Appendix F of the full dossier assessment.

Functional independence (WeeFIM)

In Study 206, no significant difference between treatment groups was shown for the outcome of functional independence, recorded with the WeeFIM. For Study 301, no suitable data are available. This results in no hint of an added benefit of vosoritide + BSC in comparison with BSC; an added benefit is therefore not proven.

Coping and beliefs (QoLISSY)

The outcomes of coping and beliefs (QoLISSY) were recorded exclusively in Study 301. Suitable data are only available for children ≥ 8 years of age from the patient-reported version. No significant difference between treatment groups was found. This results in 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

QoLISSY and PedsQL

The QoLISSY and PedsQL instruments were recorded exclusively in Study 301. Suitable data are only available for children ≥ 8 years of age from the patient-reported version. There was no significant difference between treatment groups for the outcome of health-related quality of life, recorded using QoLISSY or PedsQL. 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, severe AEs and discontinuation due to AEs

In Study 206, no events occurred in the outcomes of SAEs and discontinuation due to AEs. In Study 301, there were no significant differences between treatment groups for severe AEs and discontinuation due to AEs. For the outcome of SAEs, the meta-analysis of the studies 206 and

301 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 for these outcomes.

Injection site reactions (AE)

For the outcome of injection site reactions (AE), the meta-analysis of the studies 206 and 301 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.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Study 206
  - age at baseline (24 to < 36 months versus 36 to < 60 months)
  - sex (male versus female)
- Study 301
  - age at baseline (≥ 5 to < 8 years versus ≥ 8 to < 11 years versus ≥ 11 to < 15 years versus ≥ 15 to < 18 years)
  - sex (male versus female)

In Study 206, the only prespecified subgroup characteristic was the age at screening, according to which the 3 cohorts were formed. Only Cohort 1 of Study 206 is relevant for the present benefit assessment. The company therefore conducted post hoc subgroup analyses for this subpopulation of the study for the characteristic of age at baseline. It is unclear whether the cut-off value of 36 months for the characteristic of age is meaningful in the present therapeutic indication. For the present benefit assessment, however, the subgroup results on age in the relevant subpopulation are nevertheless considered in order to examine whether there were relevant effect modifications that contradict a meta-analytical summary of the results of Study 206 and Study 301 (see Section I 3.2).

In Study 301, all subgroup analyses were only prespecified for the outcomes of annualized growth velocity, height (z-score) and upper to lower body segment ratio. The company did not conduct subgroup analyses for all outcomes in the outcome category of side effects. This is appropriate because in some cases there were only few events.

In its dossier, the company presented the subgroup characteristic of baseline height (z-score) (≤ −4 versus > −4 for Study 206, and ≤ −6 versus > −6 to ≤ −5 versus > −5 to ≤ −4 versus > −4 for Study 301). This characteristic is suitable for reflecting disease severity in this therapeutic

indication. The cut-off values were prespecified for Study 301, but it is unclear whether the limits shown are meaningful. Therefore, the subgroup characteristic of baseline height (z-score) with the presented cut-off values is not used in the present benefit assessment.

Subgroup analyses of the meta-analytical summary of the relevant subpopulation of Study 206 and Study 301 were calculated. For the outcome of injection site reactions (AEs), no suitable data are available for Study 206 that would allow a subgroup analysis of the results pooled in a meta-analysis.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results did not show any relevant effect modifications.

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 *General Methods* of IQWiG [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).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Height (z-score)

The outcome of height (z-score) is generally to be allocated to the outcome category of non-serious/non-severe. In this therapeutic indication, however, the outcome is allocated to the outcome category of serious/severe due to the limitations and late complications resulting from the small height. The company implicitly allocated the outcome of height (z-score) to the outcome category of serious/severe by deriving an added benefit with the extent “major”.

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

Outcome category **Outcome**	**Vosoritide vs. placebo** **Proportion of events (%) or mean value/mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: -	Lesser/added benefit not proven
Morbidity		
Height (z-score)	0.27 vs. −0,01 to −0.06[c] MD: 0.28 [0.18; 0.39]; p < 0.001 Probability: “proof”	Outcome category: serious/severe symptoms/late complications Added benefit, extent: “non-quantifiable”
Functional independence (WeeFIM)		
206	12.3 vs. 11.2 MD: 1.1 [−10.44; 12.64]; p = 0.846	Lesser/added benefit not proven
301	No suitable data[d]	Lesser/added benefit not proven
Coping and beliefs (QoLISSY)		
206	Outcome not recorded	Lesser/added benefit not proven
301 Coping Beliefs	Parent-reported: No suitable data[e]	Lesser/added benefit not proven
Coping	Patient-reported: −1.92 vs. −2.26 MD: 0.34 [−11.22; 11.90]; p = 0.953	
Beliefs	5.79 vs. −2.65 MD: 8.44 [−5.13; 22.01]; p = 0.218	
Health-related quality of life		
QoLISSY[f]		
206	Outcome not recorded	Lesser/added benefit not proven
301	Parent-reported: No suitable data[e]	Lesser/added benefit not proven
	Patient-reported: 4.34 vs. −0.88 MD: 5.22 [−3.70; 14.14]; p = 0.246	

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

Outcome category **Outcome**	**Vosoritide vs. placebo** **Proportion of events (%) or mean value/mean change** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
PedsQL		
206	Outcome not recorded	Lesser/added benefit not proven
301	Parent-reported: No suitable data[e]	Lesser/added benefit not proven
	Patient-reported: 0.85 vs. −2.62 MD: 3.47 [−4.25; 11.19]; p = 0.372	
Side effects		
SAEs[g]	5.0% to 6.7% vs. 6.3% to 6.6%[c] RR: 0.82 [0.23; 2.94]; p = 0.763	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)[g]		
206	0% vs. 0% RR: –	Greater/lesser harm not proven
301	5.0% vs. 4.9% RR: 1.02 [0.21; 4.84]; p > 0.999	Greater/lesser harm not proven
Discontinuation due to AEs		
206	0% vs. 0% RR: –	Greater/lesser harm not proven
301	1.7% vs. 0% RR: 3.05 [0.13; 73.40]; p = 0.367	Greater/lesser harm not proven
Injection site reactions (AE)	80.0% to 85.0% vs. 43.8% to 82.0%[c] RR: 1.13 [0.96; 1.33]; p = 0.135	Greater/lesser harm not proven

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

Outcome category **Outcome**	**Vosoritide vs. placebo** **Proportion of events (%) or mean value/mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
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 change in each treatment arm in the included studies. d. The WeeFIM instrument is not sufficiently validated for patients > 7 years of age. The company did not present separate analyses for patients aged 5 to ≤ 7 years. e. For patients ≥ 8 years of age, health-related quality of life (PedsQL, QoLISSY), and coping and beliefs (QoLISSY) are directly represented via the patient-reported versions of QoLISSY and PedsQL. No separate analyses are available for the parent-reported version for patients < 8 years of age. f. Total score, includes the domains of physical, social and emotional. g. Including potentially disease-related events; in the present data situation, it is assumed that this does not have a relevant influence on the results. AE: adverse event; CI: confidence interval; CI_L: lower limit of confidence interval; CI_u: upper limit of confidence interval; MD: mean difference; ND: no data; PedsQL: Pediatric Quality of Life Inventory; QoLISSY: Quality of Life of Short Stature Youth; 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**
Serious/severe symptoms/late complications Height (z-score): proof[a] of added benefit – extent: "non-quantifiable"	–
No usable data are available for the outcome category of health-related quality of life for Study 206, which included children aged between 2 and < 5 years. No suitable data are available for functional independence (WeeFIM) in children aged ≥ 5 years.	
a. There is proof of added benefit at outcome level. Due to the lack of evidence or lack of positive effects in associated late complications and functional impairments, there is an indication of an added benefit in the overall assessment (see body of text below for reasons). BSC: best supportive care; WeeFIM: Pediatric Functional Independence Measure II	

For patients with achondroplasia whose epiphyses are not closed, the meta-analysis of studies 206 and 301 showed a positive effect of vosoritide treatment for the outcome of height

(z-score). The supporting consideration of the long-term data from the studies 901/301/302 (2-year comparison with placebo), 206/208 (up to 2.5 years, comparison with baseline), 301/302 (up to 3.5 years, comparison with baseline) and 202/205 (up to 7 years, comparison with baseline) shows that the effect on the outcome of height (z-score) is sustained. No conclusions can be drawn for a longer period than 7 years due to low patient numbers at the later documentation time points. Overall, the long-term data do not call into question the results of the meta-analysis of the studies 206 and 301 with regard to the benefit of vosoritide.

For the outcome of height (z-score), it is difficult to estimate what a specific change in the outcome of height (z-score) means for the individual patient. In addition, no data are yet available on patients who received vosoritide continuously from the age of 2 years until closure of the growth plates. This means that the final height that can ultimately be reached with vosoritide treatment is not yet precisely known. For the present benefit assessment, an added benefit in the outcome of height (z-score) can therefore not be quantified (see Section I 4.1).

At outcome level, there is initially proof of an added benefit for height (z-score). Based on the consideration of height (z-score), however, at best an indirect conclusion can be drawn about the effect of vosoritide treatment on the late complications and functional impairments associated with achondroplasia. However, outcomes that directly record late complications or functional impairments were not recorded in the available studies or did not show any statistically significant effects in favour of vosoritide. In addition, no suitable data are available for the other anthropometric outcomes (upper to lower body segment ratio and body proportion ratios of the extremities), which reflect achondroplasia-associated characteristics. Based on the results of the operationalization presented by the company, no change in disproportionate growth was shown, however. This results in limitations in the certainty of conclusions regarding the added benefit of vosoritide compared with the ACT BSC.

In the outcomes for which a meta-analysis of studies 206 and 301 was not possible or meaningful, there were neither positive nor negative effects of treatment with vosoritide at the level of the individual studies.

Due to the limitations described above, no more than an indication of added benefit is determined in the overall assessment.

In summary, there is an indication of a non-quantifiable added benefit of vosoritide compared with the ACT BSC for patients with achondroplasia 2 years of age and older whose epiphyses are not closed.

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] 2 years of age and older whose epiphyses are not closed	BSC[c]	Indication of non-quantifiable added benefit[d]
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 that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. d. No data are available for patients aged ≥ 15 years at the start of treatment. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee		

The assessment described above differs from that of the company, which, based on the RCTs 206 and 301 and the long-term data presented, initially derived an indication of a minor added benefit for patients aged 2 to < 5 years and an indication of 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 for all patients in the present therapeutic indication, 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.

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