Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende vosoritid til behandling af akondroplasi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. vosoritid
2. Forhandlingsnotat fra Amgros vedr. vosoritid
3. Ansøgers endelige ansøgning vedr. vosoritid

DMC assessment report of VOXZOGO® – Company response

BioMarin International Ltd (the Company) thanks DMC for its evaluation of VOXZOGO® (vosoritide). The Company welcomes the acknowledgement in the clinical section of the evaluation report that treatment with VOXZOGO® is associated with increased growth in children with achondroplasia (ACH) and that VOXZOGO® is generally well tolerated with no important safety risks identified.

However, the Company has concerns with some of the conclusions in the health economic report, and the associated adjustments to the Cost Effectiveness (CE) model initially made by the FINOSE working group and copied by the DMC assessors. In the Company's view, the adjustments are inconsistent with available data from clinical trials or clinical opinion collected during the HTA evaluation, e.g., on long-term effects which cannot be covered within current follow-up in clinical trials. The Company is concerned that with these adjustments, the evaluation does not produce the most likely estimate of the true effect of VOXZOGO® and the potential benefits achieved with the treatment. Thus, the DMC board is at risk of making an ill-informed decision whether or not the Danish society will offer an EMA approved treatment with proven efficacy to children with ACH who have no alternative treatment options.

The Company has major concerns with the evaluation, but given the size limitations of this response, the issues raised herein are not exhaustive. Furthermore, the DMC policy to exclude caregiver benefits and productivity effects results in the disregarding of societally important values contributed to by the treatment. As ACH is a rare disease, this necessitates a different assessment as compared with conditions of normal prevalence. As outlined further below, other national HTA agencies have acknowledged the value of VOXZOGO® and approved its reimbursement.

Uncertainty in CE assessment: Whilst DMC concludes that the CE results are subject to significant uncertainties, the Company wishes to stress that considering the changes to the model implemented by DMC, the CE results presented in the DMC report, including the ICER, do not represent a midpoint of the range of uncertainty, but rather the very conservative upper end of it.

QoL in ACH: DMC's assessment of the QoL in ACH is a major concern for the Company. The Company does not agree with the adjustments that DMC has implemented in the QoL utility modelling in the CE model which result in DMC underestimating the burden of untreated ACH and the QoL decrement from ACH, which in turn has a direct impact on the cost-effectiveness assessment.

Firstly, the assessment report provides an inaccurate critique of the QoL modelling, since the statement that QoL utility is modelled independently of age and gender is incorrect. The Company wants to clarify that the utility is modelled as a function of HSDS (height standard deviation score) which is a gender and age normalized measure. Furthermore, utility values are age adjusted in the CE model, and the model separately accounts for disutility associated with complications. The impact of age and complications are supported by a time-trade off study,[1] which showed that utilities were lower when members of the general population were presented with vignettes describing older ACH patients with more complications.

Secondly, the Company questions DMC's changes to the regression model used to estimate QoL utility by HSDS in the CEM. DMC applies a linear regression model including all data points (from +2.75 to -3.25 HSDS) in the Christensen 2007 dataset,[2] although the data (Figure 3-3 in the DMC report) indicate a trend shift around -2 HSDS, with a steeper decrement in utility below this point. The Company's submission included a sensitivity analysis with an alternative linear utility model fitting a linear regression to the three lowest HSDS data points (from -2.25) in the dataset which were considered most relevant from a short stature perspective. When DMC judged the quadratic regression to be unfit to use, this alternative linear model would have been a relevant alternative. Applying the Company's alternative linear model together with DMC's all other model adjustments generates an ICER of 2,357,000 DKK/QALY calculated with AIP.

Thirdly, the Company questions the relevance of using diseases such as diabetes and asthma to benchmark QoL in ACH, a chronic and debilitating disorder. In addition to severe disproportionate short stature, ACH is associated with multiple complications throughout the lifetime, some of which may require invasive corrective surgery. DMC also refers to QoL outcomes from the LIAISE study for the validity of their approach. However, the utility value reported in LIAISE is based on the EQ-5D which is considered insensitive to measuring QoL in ACH due to issues such as the disability paradox whereby patients with achondroplasia experience adaptation effects, and consider themselves to be in better health than if members of the general population rated their health state. Furthermore, the EQ-5D in LIAISE was administered to adult patients who are particularly prone to adaptation effects. For the above reasons, the Company does not consider the LIAISE data to be relevant for validation of the QoL utility in ACH. This is further supported by consulted Danish clinical experts[3] who saw a risk that the QoL benefit from VOXZOGO® treatment would be underestimated using the regression analysis of the Christensen data, rather than overestimated as suggested by DMC.

Treatment effect on medical complications of ACH: The Company would like to stress that by entirely removing the impact of VOXZOGO® on complications, DMC is likely significantly underestimating the value of VOXZOGO® over a patient's lifetime. Many of the complications associated with ACH such as foramen magnum stenosis, spinal stenosis and genu varum are caused by inhibition of endochondral bone growth (the underlying cause of ACH). Data from Phase III and II clinical trials demonstrate the meaningful and sustained growth achieved by patients treated with VOXZOGO®. An assumption that the restoration of growth will lead to a reduction in the incidence and severity

of complications relating to restricted endochondral bone growth is supported by consideration of the disease process and the mechanism of action of VOXZOGO®, and the expectation of both international and Danish clinical experts.

The Company objects to the DMC's statement that there is no available evidence for a direct impact of VOXZOGO® treatment on complications. Preliminary data from the Phase II 206 trial report changes in patients aged 0-6 months with respect to MRI parameters of facial volume, sinus volume and foramen magnum area[4], pointing to a potential benefit of VOXZOGO® beyond linear growth in this age group. Please note, the impact of VOXZOGO® on foramen magnum stenosis is being investigated in an ongoing study (111-209) in children with ACH <1 year of age who are at high risk of requiring surgical decompression. Also, a modified Delphi panel was conducted in 2021 consisting of clinical experts with decades of expertise in ACH.[5] This provides a significant source of expertise which is captured under the aegis of a Delphi panel, and is thus officially recognized as level 4 evidence (as per SIGN guidelines of evidence hierarchy). The Delphi Panel explored the perceived impact of ACH on medical complications, HRQoL, healthcare resource use and mortality which was based on published evidence and expert opinion. Finally, it's important to understand that many of the consequences of restricted endochondral growth arising from ACH manifest in adulthood, many years or decades after the opportunity to intervene and restore growth has passed. Inevitably, it is challenging to generate evidence on the effectiveness of VOXZOGO® in relieving ACH-related complications, given the rarity of the disease and the timescales involved. Considering the high unmet need within ACH, it does not seem reasonable nor practical to require patients to wait for decades for long-term data on complications before getting access to treatment.

Starting age in CEA: The Company disagrees with DMC's decision to implement a starting age between 2-12 years old in the model. While in the short-term (in the first 1-2 years after VOXZOGO® becomes available), it is expected that patients of different ages within the prevalent cohort will start treatment, once these older patients have started treatment, only patients turning 2-yrs old will be initiated each year. Considering this point, and the fact that the youngest patients are expected to derive the highest benefit from VOXZOGO® treatment with respect to height, QoL and complications over their lifetimes, it's critical that the value of VOXZOGO® treatment for the younger population is appropriately captured in the economic model.

Clinical evidence of long-term efficacy: The Company believes that DMC's presentation fails to fully acknowledge the available clinical evidence supporting the long-term efficacy of VOXZOGO®. Data from 7.5 years of follow-up showing consistent, sustained growth should be considered a more robust dataset than generally available for the typical innovative orphan drug. It's important to recognize that for a patient to have received treatment with VOXZOGO® from 2 years of age until epiphyseal closure, a trial spanning >14 years would be required. This is an unrealistic and implausible requirement for an orphan drug that is targeting a lifelong disorder with significant medical unmet needs, particularly where no other treatment exists that addresses the underlying cause of ACH.

Furthermore, the Company does not agree with the DMC conclusion that the magnitude of the increase in growth with VOXZOGO® relative to comparator is unknown. For ethical reasons, a placebo-controlled long-term trial would not be considerable when the efficacy of the treatment has been established. But for ACH, being a genetic disorder with predictable, objective and well studied natural history outcomes, available natural history data provide a very relevant and valid source of comparative data.

Error in the presented results of sensitivity analyses: In Table 3-4, the results for "Applicant's main analysis" doesn't match the results from the Company's submission dossier. The DMC report states: Incr QALY: 3.876, Incr Cost: 6,417,060 DKK, ICER: 1,655,580 DKK/QALY; but the results in the Company's base case were: Incr QALY: 9.46, Incr Cost: 12,454,966 DKK, ICER: 1,316,162 DKK/QALY.

Discounting: The description of the model's discounting in the DMC report is simplified and may give the impression that the CE model deviates from the DMC policy. In fact, the correct discounting approch is implemented in the CE model: 3.5% for year 0-35; 2.5% for year 36-70: 1.5% for year 71+.

Assessments made in other countries: Several HTA bodies and payers have reported evaluations of VOXZOGO® with different conclusions than DMC, including Germany[6] where G-BA established a hint for a non-quantifiable additional benefit; Australia[7] where the PBAC considered VOXZOGO® to offer high therapeutic value and allowed a starting age from zero for all patients in the CE model; France[8] who deemed ACH to be a rare and serious condition and VOXZOGO® to offer substantial clinical benefit; and Italy[9] who awarded VOXZOGO® innovative status which implies a positive therapeutic need, added therapeutic value and robustness of the scientific evidence.

References

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24.01.2024
CAF/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.02.2024
Leverandør	Biomarin
Lægemiddel	Voxzogo (vosoritide)
Ansøgt indikation	Behandling af akondroplasi hos patienter på 2 år og derover, hvor epifyserne ikke er lukkede. Diagnosen akondroplasi skal bekræftes ved hjælp af relevant gentest.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Voxzogo (vosoritide):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Voxzogo	400 µg 560 µg 1200 µg*	10 hætteglas	35.250	[redacted]	[redacted]

*Voxzogo findes i tre forskellige styrker og pakninger. Pris pr. pakning er den samme uanset styrke.

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Voxzogo, indkøbes det til AIP.

Aftaleforhold

Amgros har ved forhandling fået ovenstående pris fra leverandøren, som er betinget af Medicinrådets anbefaling af Voxzogo til den ansøgte indikation. Da flere leverandører har udtrykt, at de kan levere Voxzogo har Amgros publiceret et udbud med tilbudsfrist den 26.02.2024.

[redacted]

Aftalen kan starte den 01.06.2024 med mulighed for prælevering så snart aftalen er underskrevet af leverandøren.

Konkurrencesituationen

Der er på nuværende tidspunkt ikke andre lægemidler, som er godkendt til samme indikation, men det forventes at EMA vil godkende flere lægemidler herunder Navepegritide, der forventes godkendt i august 2026.

Lægemiddel	Styrke	Pakningsstørrelse	Dosering**	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Voxzogo	400 µg 560 µg 1200 µg	10 hætteglas	0-26,67 kg 26,67-37,33 kg 27,33-80 kg	[redacted]*	[redacted]

*Prisen for hver af de tre doser er den samme, og derfor er lægemiddeludgiften for behandlingen den samme for alle børn, der vejer under 80 kg.

**15µg/kg hver dag

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til vurdering
Sverige	Ikke anbefalet	Beslutning baseret på FINOSE rapport.	FINOSE rapport
England	Under vurdering		Link til vurdering
Finland	Ikke anbefalet	Beslutning baseret på FINOSE rapport.	

Konklusion

[redacted]

Medicinrådet

Application for the assessment of VOXZOGO® (vosoritide) for achondroplasia

2023-08-29

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table of contents

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Color scheme for text highlighting	
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1. Basic information

Table 1. Contact information

Contact information	
Company	**BioMarin International Limited**
Name	Søren Hansen
Title	Associate Country Manager, Denmark & Iceland
Responsibility	Responsible for Denmark and Iceland
Phone number	+45 61199008
E-mail	soren.hansen@bmrn.com
External representation	Name/company: NA
	Phone number/e-mail: NA

Table 2. Overview of the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	VOXZOGO®
Generic name	vosoritide
Marketing authorization holder in Denmark	BioMarin International Limited
ATC code	M05BX07
Pharmacotherapeutic group	Drugs for treatment of bone diseases
Active substance(s)	vosoritide
Pharmaceutical form(s)	Powder and solvent for solution for injection.
Mechanism of action	Vosoritide is a modified type C natriuretic peptide (CNP). In patients with achondroplasia, endochondral bone growth is negatively regulated due to a gain of function mutation in fibroblast growth factor receptor 3 (FGFR3). Binding of vosoritide to natriuretic peptide receptor-B (NPR-B) antagonises FGFR3 downstream signalling by inhibiting the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the mitogen-activated protein kinase (MAPK) pathway at the level of rapidly accelerating fibrosarcoma serine/threonine protein kinase (RAF-1). As a result, vosoritide, like CNP, acts as a positive regulator of endochondral bone growth as it promotes chondrocyte proliferation and differentiation [1].
Dosage regimen	***Form of administration:*** Daily subcutaneous injection [1]. ***Dosage regimen:*** It is important to initiate treatment in children as young as possible [1]. The volume of vosoritide to be administered at the recommended dose is based on the patient's weight and the vosoritide concentration (see table below). The usual dose is 15 µg/kg body weight. For practicality reasons and to account for weight-related pharmacokinetics changes (see section 5.2 of SMPC), the following dosing is recommended [1]:

Overview of the pharmaceutical

Body weight (kg)	Vosoritide 0.4 mg solvent (water for injections): 0.5 mL concentration: 0.8 mg/mL	Vosoritide 0.56 mg solvent (water for injections): 0.7 mL concentration: 0.8 mg/mL	Vosoritide 1.2 mg solvent (water for injections): 0.6 mL concentration: 2 mg/mL
	Daily injection volume (mL)		
10-11	0.30 mL		
12-16		0.35 mL	
17-21		0.40 mL	
22-32		0.50 mL	
33-43			0.25 mL
44-59			0.30 mL
60-89			0.35 mL
≥ 90			0.40 mL

Duration of treatment:

Treatment with this medicinal product should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses [1].

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	VOXZOGO® is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing [1].
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	No
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	• 10 vials × 0.4 mg powder and solvent for solution for injection • 10 vials × 0.56 mg powder and solvent for solution for injection • 10 vials × 1.2 mg powder and solvent for solution for injection
Orphan drug designation	On 24 January 2013, orphan designation (EU/3/12/1094) was granted by the European Commission to BioMarin Europe Ltd, for modified recombinant human C-type natriuretic peptide for the treatment of achondroplasia. The sponsorship was transferred to BioMarin International Limited, in February 2019.

2. Abbreviations

Abbreviation	Definition	Abbreviation	Definition
ACH	Achondroplasia	**ITQoL**	The Infant Toddler Quality of Life Questionnaire
AchNH	Achondroplasia natural history multicentre clinical study	**LIAISE**	Lifetime Impact of Achondroplasia Study in Europe
ADL	Activities of daily living	**LISA**	Lifetime Impact Study for Achondroplasia
AE	Adverse event	**LS**	Least square
AGV	Annualised growth velocity	**MAPK**	Mitogen-activated protein kinase
ALP	Alkaline phosphatase	**MedDRA**	Medical Dictionary for Regulatory Activities
ANCOVA	Analysis of covariance	**MRI**	Magnetic resonance imaging
ATC	Anatomical Therapeutic Chemical	**N/A**	Not applicable
BIM	Budget Impact Model	**NFAH**	Near final adult height
BMI	Body mass index	**NH**	Natural History
BSID-III	Bayley Scales of Infant Development	**NPPC**	Natriuretic peptide precursor C
CBCL	Child Behaviour Checklist	**NPR-B**	Natriuretic peptide receptor B
CDC	Centers for Disease Control and Prevention	**OSA**	Obstructive sleep apnoea
cGMP	Cyclic guanosine monophosphate	**PedsQL**	Pediatric Quality of Life Inventory
CI	Confidence interval	**PK**	Pharmacokinetics
CNP	C-type natriuretic peptide	**PLC**	Placebo
CSR	Clinical Study Report	**PY**	Person years
CTCAE	Common Terminology Criteria for Adverse Events	**QALY**	Quality-adjusted life year
CVD	Cardiovascular Disease	**QD**	Once daily
DXA	Dual X-ray absorptiometry	**QoL**	Quality of life
DMC	Danish Medicines Council	**QoLISSY**	Quality of Life in Short Stature Youth
ECG	Electrocardiogram	**RCT**	Randomised controlled trials
eCRF	Electronic case report form	**SAE**	Serious adverse events
EMA	European Medicines Agency	**SDS**	Standard deviation score
ENDO	Endocrine society annual meeting	**SLR**	Systematic literature review
ENT	Ear, nose and throat	**SmPC**	Summary of product characteristics
EQ-5D-5L	EuroQol-5 Dimension-5 Levels	**SMQ**	Standardised MedDRA Query Analysis
FAH	Final adult height	**TEAE**	Treatment emergent adverse event
FAS	Full analysis set	**TRAE**	Treatment-related adverse event
FGF	Fibroblast growth factor	**TRSAE**	Treatment-related serious adverse event
FGFR3	Fibroblast growth factor receptor 3	**UK**	United Kingdom
FM	Foramen magnum	**US**	United States
GH	Growth hormone	**VOS**	Vosoritide
GP	General practitioner	**WeeFIM**	Functional Independence Measure for Children
HCP	Healthcare professionals	**Yr**	Year
HCRU	Healthcare resource use		
HRQoL	Health-related quality of life		
IAF	Informed assent form		
ICF	Informed consent form		
IGF	Insulin-like growth factor		
IQR	Inter-quartile range		

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3. Tables and Figures

List of tables

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

List of figures

4. Executive Summary

4.1 Disease background and burden

Achondroplasia (ACH) is a rare progressive, autosomal dominant genetic disorder that affects approximately 250,000 people worldwide, in which a mutation in the FGFR3 gene causes impaired endochondral bone formation in the long bones, ribs and vertebrae [2]. Achondroplasia is most frequently diagnosed before or shortly after birth based on clinical characteristics and is typically confirmed using genetic testing [2, 3].

Due to impaired bone formation, patients with ACH experience extreme short stature (approximately 5.0 - 7.0 standard deviations (SD) below average stature, in adulthood) and disproportionality, which substantially reduces their mobility and reach [4, 5]. Furthermore, patients with ACH experience a range of lifelong, serious, and debilitating symptoms and complications which progress and evolve over time; these frequently include orthopaedic; neurological; respiratory; ear, nose and throat (ENT); and dental problems [2, 6]. Neurosurgical and orthopedic complications may lead to motor deficits in the upper and lower limbs and to compensatory walking predisposing to moderate or severe chronic pain, especially in adulthood [2, 7, 8]. In patients with ACH, the final adult height is approximately 125.0 cm in females and 130.0 cm in males [2].

Patients with ACH are often not able to independently conduct activities of daily living (ADL) such as self-care and hygiene tasks, largely related to impaired mobility and reach [8, 9]. Many patients also face chronic pain as a result of their symptoms, which further impairs functional independence and places a burden on everyday life. Quality of life (QoL) among the ACH population, including in paediatric and adult patients, is substantially reduced compared to average stature individuals. Importantly, correlations between QoL and height outcomes such as final adult height (FAH) and height Z-score in ACH patients have been demonstrated in several studies using a range of QoL measures [10-12]. These results indicate that height has a substantial impact on QoL and functional dependence associated with ACH, and that improved height-related outcomes lead to meaningful improvements to ACH patients' lives.

Patients with ACH frequently experience impaired school functioning, restricted employment options, increased risk of unemployment, and impaired productivity compared with unaffected individuals as a result of their condition [9, 13, 14]. Carers and families of patients with ACH are also burdened, facing reduced QoL and impaired or restricted productivity and capacity to travel [15]. Furthermore, the extensive management of symptoms and comorbidities required by patients with ACH are expected to lead to a higher healthcare resource use (HCRU) compared with the general population. This is primarily driven by multiple surgeries in younger patients, and heavy reliance on symptomatic medications in older age groups.

In addition, patients with ACH experience a substantially higher risk of death in their first year of life compared with the general population, primarily due to foramen magnum stenosis and cervicomedullary compression, and invasive surgery is often required to mitigate this risk [16-18]. For ACH patients who survive into adulthood, the average life expectancy is approximately 10 years shorter than the general population, and mortality associated with heart disease is estimated to be more than 10 times greater amongst young adults with ACH compared with average stature individuals [16, 18].

4.2 Epidemiology

ACH occurs in 1 per 20.000 - 30.000 livebirths and this gives an estimate of approximately 200 people with ACH in Denmark, whereof 32 of those patients in an age span relevant for vosoritide treatment [7, 17]. According to the ACH reference centres in Denmark the number of ACH patients between 2 and 14 years is [redacted] with Aarhus centre reporting [redacted] [19] and Copenhagen centre reporting [redacted] [20]. Based on the birth prevalence, it is estimated that approximately 2-3 new ACH patients are born in Denmark each year, and all cases are being diagnosed at birth. The number of eligible patients is expected to remain constant though, given that approximately the same number of patients enter and leave the relevant age span each year.

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4.3 Current management and unmet need

Prior to the approval of vosoritide there was no licensed treatment available addressing the underlying cause of ACH. Instead, patients with ACH rely on invasive surgical procedures and medications to manage the evolving range of symptoms and complications that they experienced throughout their lives. As such, there are no treatment guidelines in place for the management of ACH in Denmark. Furthermore, vosoritide is an innovative treatment with no therapeutic equivalent existing comparator.

National disease management guidelines differ substantially across geographies, resulting in inconsistent and sub-optimal treatment for patients with ACH [4, 21]. Some geographies utilise limb lengthening surgery with the aim of increasing height, but these prolonged procedures do not address the underlying cause of disease and only target the long bones. Limb lengthening is associated with substantial pain and a considerable risk of severe complications including infections, fractures, and a reduced range of motion [4, 21]. As confirmed by consulted clinical experts, limb lengthening is very rarely performed in Denmark and is not recommended by Danish clinical experts [19, 20].

There remains a substantial unmet medical, humanistic and economic need for an efficacious and well-tolerated pharmacological treatment for ACH which address the underlying cause of impaired endochondral ossification/ bone formation, improves height and reach and reduces the burden of associated disease symptoms and comorbidities.

4.4 Product information

Vosoritide is a stabilised biological analogue of C-type natriuretic peptide (CNP) and is the first and only licensed pharmacological treatment which targets the effect of the underlying *FGFR3* gene mutation in order to improve endochondral bone growth [1, 22].

Vosoritide is administered as a daily subcutaneous (SC) injection, and can therefore be taken by patients in the comfort of their own home [1].

Vosoritide has been granted Orphan Drug Designation by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), highlighting the rarity of disease and the considerable need for a novel treatment option for ACH that targets the underlying cause of the disease [23, 24].

The approved indication of vosoritide in EU is for the treatment of ACH in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of ACH should be confirmed by appropriate genetic testing [1].

4.5 Clinical evidence

The efficacy and safety of vosoritide has been investigated within an extensive and robust clinical development programme, which includes the pivotal Phase III (study 111-301 and extension study 111-302) randomised, double-blind, placebo-controlled trials (RCTs) and Phase II (study 111-202 and extension study 111-205, Study 111-206 and extension study 111-208), as well as non-interventional natural history studies conducted in patients aged 0–18 years and adults (Study 111-901 and study 111-501). Available results in patients aged 2–18 years show that vosoritide consistently met the primary endpoints of the studies [22, 25-29].

In Phase II (111-202/205) and Phase III (111-301/302) trials, ACH patients aged 5–14 years and 5- 18 years respectively, treated with vosoritide showed significant improvements in height outcomes (annualised growth velocity [AGV] and height Z-score) compared with untreated natural history populations (in 111-202) and placebo-treated patients (in 111-301) [22, 27]. In line with the observed increases in AGV, consistent and clinically meaningful improvements in height Z-score were also observed in ACH patients treated with vosoritide [30, 31]. Available efficacy data from the Phase II studies 111-206 and extension study 111-208 of vosoritide in age groups 0 to < 6 months, ≥ 6 to < 24 months, ≥ 24 to < 60 months and > 60 months, suggests consistent positive trends in growth following vosoritide treatment in patients aged ≥ 6 to < 60 months as well as a similar safety profile to that of patients > 5 years [29, 32].

Comparative analyses conducted between clinical trial data (studies 111-201/205 with 7.5 years follow-up and 111-301/302 with 3 years follow-up) and natural history studies support the long-term clinical benefit of vosoritide [33]. These analyses demonstrated a significant incremental height gain of 9.08 cm among patients treated with vosoritide over five years compared to untreated individuals, placing the mean AGV of patients who received vosoritide within the same range as peak AGV for average stature children in the United States (US) [28, 33, 34]. Assuming an average 2 cm/year deficit in AGV among pre-pubertal children with ACH compared to their average stature counterparts, the improvement in AGV as a result of vosoritide treatment represents a restoration of around 75% of this growth deficit [22, 30, 35]. Furthermore, the observed increase in growth occurred proportionally in both the spine and the lower limbs [30], with a trend towards improved upper to lower body proportionality [29, 30].

Alongside these significant clinical benefits, vosoritide has shown a strong tolerability and safety profile across all trials, with low incidences of treatment-related serious adverse events (SAEs), and no trial discontinuations due to adverse events (AEs) reported. Despite vosoritide leading to improved height, no evidence has been found for changes in bone morphology or accelerated progression of bone age with vosoritide treatment [22, 25-29, 33].

4.6 Benefits of treatment

Several studies have assessed the impact of short stature on health-related quality of life (HRQoL). The LIAISE (111-501) natural history study found that greater height was associated with better QoL and functionality in children with ACH [9]. Moreover, an exploratory post-hoc analysis of data on height Z-score and HRQoL pooled from studies 111-901, 111-301 and 111-302 demonstrated a clear correlation between the magnitude of height deficit (Z-score) and HRQoL relating to the Physical and Social domain scores [36, 37]. Together these analyses suggest that improved height with vosoritide treatment is likely to lead to meaningful and durable improvements in patients QoL. Improved proportionality and symptom burden is also likely to result in substantial improvements to functional independence and ADL as well as simultaneously reducing the healthcare resource use (HCRU) of patients [36, 37].

Therefore, by addressing endochondral bone formation and improving height, vosoritide could potentially demonstrate effectiveness on certain other complications and quality of life in individuals with ACH.

All patients have the capacity to benefit from continued vosoritide treatment until growth stops (epiphyses close), with extrapolations of trial data from 111-205 demonstrating that patients treated with vosoritide have substantially improved FAH compared to untreated natural history ACH populations.[38]

4.7 Economic aspects

The cost-effectiveness evaluation was undertaken using an individual simulation model, which captures the impact of reduced stature on QoL and the incidence of complications related to ACH over the lifetime of the patient. An individual simulation model was considered the best approach to capture the varying disease courses across people with ACH and the sequalae of complications. The economic evaluation captured the impact of both reduced stature and complications associated with ACH on QoL. The base case analysis was performed over a lifetime horizon, with 1-year cycles. Growth was simulated throughout childhood according to the natural variation observed in children with ACH and the impact of treatment with vosoritide in the age span from 2 to 15 years, i.e. until growth plate closure for the average patient. Clinical experts indicate that on average, epiphyseal closure occurs between 14-16 years old in females and 15-17 years old in males, which is also supported by literature [39]. As the model requires an average stopping age across genders, 15 years old was taken as an average. Health effects were estimated in the model as quality-adjusted life years (QALYs), modelling the impact of reduced stature on QoL as well as the impact of complications associated with ACH on QoL [40]. The incidence and sequalae of the most important complications were modelled both under SoC and after treatment with vosoritide, where the likelihood of complications was modelled as a function of the extent of growth retardation. Consequently, complication risks varied between patients and according to their treatment status.

The base-case estimate of cost-effectiveness was that treatment with vosoritide from the age of 2 years generates a discounted gain of 9.46 quality-adjusted life years (QALYs) at an increased cost of [redacted] per patient, resulting in an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY. Sensitivity analyses indicated that the results are sensitive to assumptions on the discount rate, where the undiscounted analysis indicated an ICER of [redacted] per QALY. Other driving parameters, although with substantially lower impact than the discount rates, were the vosoritide drug cost, the AGV improvement rate with vosoritide treatment and the coefficients in the quadratic model for HSUV by z-score, while the results are relatively insensitive to assumptions on the impact of treatment on the risk of complications. Scenario analyses assuming alternative ages at commencement and termination of treatment generate broadly similar estimates of cost-effectiveness. In the probabilistic sensitivity analysis, the overall QALY gains ranged between 10.03 and 11.77 QALYs across simulations.

The budget impact was estimated based on the average birth prevalence of ACH, the average live birth rate in Denmark over the past years, Danish clinical experts' expectations for treatment rates, and the uptake rates observed in other European markets. The number of patients expected to be treated with vosoritide in the upcoming years was thus estimated to be 22 patients in year 1, increasing to 29 patients in year 5. With the annual treatment cost with vosoritide based on the submitted pharmacy retail price, and ACH related annual health care costs sourced from the CE model, the estimated budget impact was an added annual expenditure of [redacted] in year 1, increasing to [redacted] in year 5, if vosoritide is recommended as a standard treatment. The increased cost is predominantly associated with increased treatment costs, while some savings in health care costs are expected.

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5. The patient population, the intervention and choice of comparator(s)

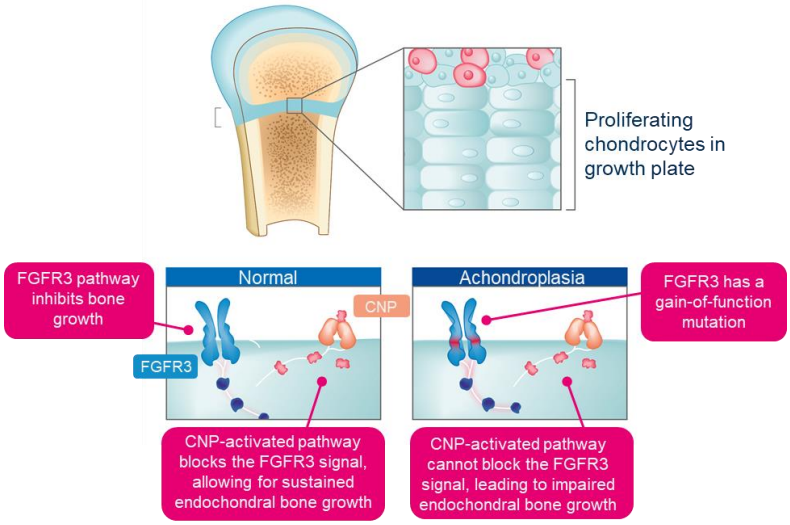
5.1 The medical condition and patient population

ACH is the most frequent form of rhizomelic dwarfism, which is a congenital disease that affects the formation of bone and/or cartilage. It is a rare and progressive genetic disorder characterized by inhibition of endochondral bone growth, resulting in small disproportionate stature with abnormal bone growth, and a progressive range of potentially severe symptoms and comorbidities throughout patients' lives [41, 42].

5.1.1 Aetiology and pathophysiology

Endochondral ossification is highly regulated by a number of molecular pathways, including fibroblast growth factor (FGF) and mitogen-activated protein kinase (MAPK) signaling pathways. In normal growth and development, these highly regulated signaling pathways help ensure normal bone growth resulting in average stature [43-45].

Figure 1. Endochondral ossification with normal versus mutated *FGFR3*



Abbreviations: CNP: C-type natriuretic peptide; FGF: fibroblast growth factor; FGFR3: fibroblast growth factor receptor 3; MAPK: mitogen-activated protein kinase. Figure adapted from Ornitz DM, Legeai-Mallet L. 2017[46]

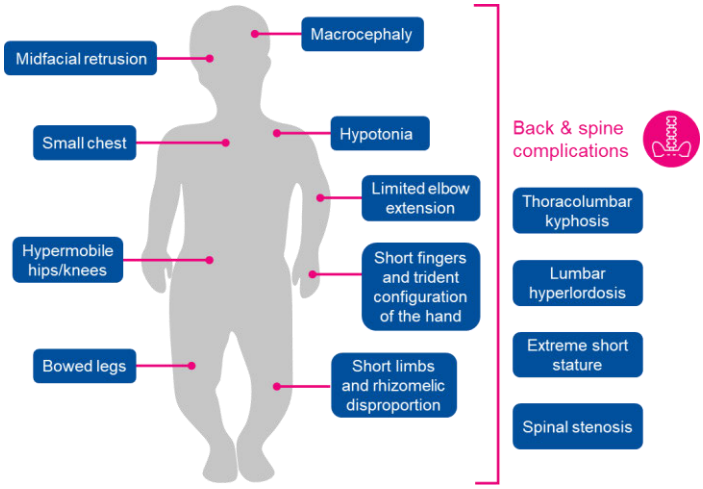
ACH is caused by a recurrent mutation in the *FGFR3* gene, leading to persistent tyrosine kinase activity (an intracellular component of the transmembrane receptor FGFR3) and therefore overactivation of the downstream MAPK pathway (Figure 1) [47]. Regulation of endochondral bone growth results in reduced endochondral ossification of ribs, long bones and vertebrae and, consequently, disproportionate growth [44, 48, 49].

Approximately 20% of cases of ACH are the result of a mutation transmitted by a parent with the disease, and the remaining 80% of cases are individuals with average-sized parents, the causal mutation being a spontaneous variant (*de novo)* [7].

5.1.2 Clinical symptoms and severity of the disease

Clinically, ACH is characterized by macrocephaly with frontal bossing, as well as short limbs with rhizomelic shortening (selective disproportionate shortening of the proximal parts of the limbs i.e., humerus and femur), as seen in Figure 2. People with ACH reach a mean height of 130.0 cm for men and 125.0 cm for women, compared to 176.5 cm for men and 163.0 cm for women in the general population [5, 50, 51]. The annualized growth rate (AGV) is lower in patients with ACH. From 0 to 16 years of age, the AGV for children with ACH is about 5 cm per year, compared to 7 to 9 cm per year in children without ACH [34].

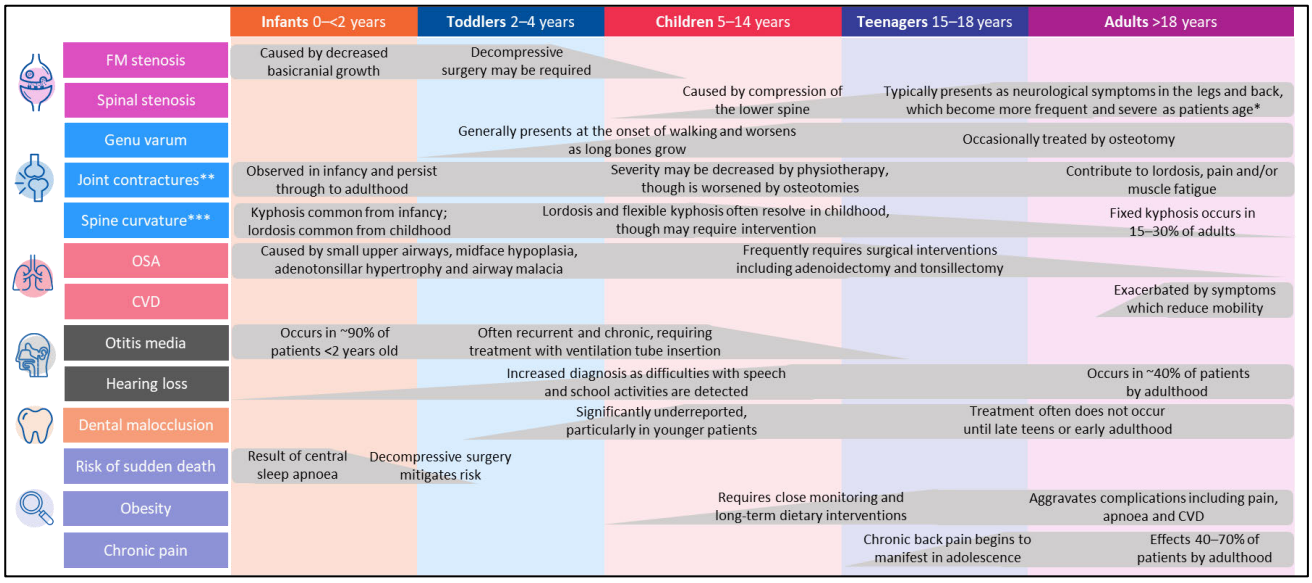
Figure 2. Overview of the clinical features of ACH



Abbreviations: FGFR3: fibroblast growth factor receptor 3. Source: Adapted from Pauli RM. 2019 [2],. Merker 2018 [5]

ACH is a complex disease that progresses over the course of a patient's life and affects many systems in the body (Figure 3). The alteration of endochondral bone formation in patients with ACH causes abnormal bone growth throughout the body and generates multiple associated clinical repercussions, usually present from birth and in early childhood, of which the most characteristic is the severity of the stature delay [2]. Abnormal bone growth in these patients is also associated with severe symptoms and complications occurring more frequently than in the general population [6, 18, 41, 48]. The most frequently observed symptoms and complications according to the age of patients with ACH are presented in Figure 3.

Figure 3. Summary of the most common symptoms and comorbidities observed by age in patients with ACH



Abbreviations: CVD: cardiovascular disease; ENT: ear, nose and throat; FM: foramen magnum; OSA: obstructive sleep apnoea.
**Due to factors associated with ACH-specific ageing such as disc protrusion, spondyloarthritic spurs, a kyphotic wedge, excess lumbar lordosis (perhaps exacerbated by excess weight), a bulging annulus fibrosis, and vertebral malalignment/instability.*
***Hip and elbow flexion contractures.*
****Lumbar hyperlordosis and thoracolumbar kyphosis*
Sources: Horton et al. 2007 [48], Hunter et al. 1998 [6], Ireland et al. 2014 [41], Simmons et al. 2014 [52], Okenfuss et al. 2020 [53], Wynn et al. 2007 [16], Hecht et al. 1987 [54], Hecht et al. 1988 [55], Fredwall et al. 2020 Sources : Horton et al. 2007 [48], Hunter et al. 1998[6], Ireland et al. 2014 [41], Simmons et al. 2014 [52], Okenfuss et al. 2020 [53], Wynn et al. 2007 [16], Hecht et al. 1987 [54], Hecht et al. 1988 [55], Fredwall et al. 2020 [56].

Infants 0- 2 years

During the first year of life, patients with ACH have a higher risk of death due to foramen magnum stenosis (narrowing of the opening at the base of the skull allowing the passage of neurological pathways from the brainstem to the cervical spinal cord) with potential cervicomedullary compression. The narrow foramen magnum can cause compression of the brainstem, spinal cord, and vertebral veins and arteries, contributing to the mortality rates observed in these patients from sudden death (2–7.5%) [2, 54]. High cervical-medullary compression also leads to possible central sleep apnea. Finally, sleep-disordered breathing has been reported in 67% of infants with ACH and is related to the narrowing of the upper airway as a result of skull base growth defects and mid-facial retrogression. This concomitant increase in apneic events with a decrease in the response to arousal are also a cause of sudden death in patients during the first year of life [57]. Invasive surgery to reduce compression is sometimes needed to reduce this risk in infants with ACH [17].

Furthermore, a total of 90% of patients with ACH have otitis media before their second birthday, and among those who experience it in their first year of life, 25% would develop chronic and recurrent otitis media. At least one third of children aged 1 to 2 years with ACH should have a ventilation tube insertion procedure [6, 58].

Infants with ACH also frequently have developmental delays, including axial hypotonia in the early years and delayed oral language acquisition. Global motor delays are linked to mild to moderate hypotonia (decreased muscle tone) often seen inACH patients and is possibly aggravated by the cervicomedullary compression associated with foramen magnum stenosis [2, 48, 59].

(Infants 0-2 years are currently not included in the vosoritide indication)

Toddlers 2- 4 years

In patients aged 2 to 4 years, upper airway obstruction, sleep breathing disorders and obstructive sleep apnea (OSA) remain a frequent risk, for which surgery to prevent the impact of upper airway obstruction (including adenoidectomy, turbinectomy, and tonsillectomy) is necessary in many of these patients. If OSA persists, non-invasive ventilation with continuous positive airway pressure may be necessary [6].

In small infants, there is often a dorsolumbar kyphosis that requires the use of a small corset from the age of 9 months, until the acquisition of walking. With age, the acquisition of walking, hyperlaxity of the knees and sometimes excess weight, can cause bowing of the legs called genu varum. This can start as early as 2-3 years of age and be seen in approximately 40% of toddlers with ACH, and progresses rapidly between the ages of 3 and 4 years [60]. This symptom is associated with discomfort or pain when walking.

Children 5-14 years

Throughout the pediatric age, the impact of impaired endochondral bone growth remains significant. OSA is the most common respiratory disorder, occurring in 20–54% of patients from the first year of life and often requiring long-term treatment [61, 62]. Sleep apnea is also associated with later pathological effects, such as an increased cardiovascular risk, overweight, impaired concentration and daytime vigilance, resulting in a probable increase in accidents due to lack of sleep [2].

Teenagers 15-18 years and adults >18 years

Many of the complications that develop in infancy and childhood continue to affect patients with ACH throughout their (adolescence and adult) lives. Additionally, the impact of chronic otitis media throughout infancy is exacerbated in adolescents, resulting in hearing loss in approximately 25% of patients before the age of 18 [6, 63]; it is also present in a significant number of adults [64].

5.1.2.1 Risk of mortality

Due to the abnormal endochondral bone growth, individuals with ACH suffer elevated risk of sudden death, higher risk of infant mortality and a reduced overall life expectancy [2, 54, 65]. Mortality remains worrying with a risk of sudden death in patients aged 1 to 4 years of approximately 2.5% [54]. American studies also show an overall average life expectancy of patients with ACH reduced by 10 to 15 years compared to the general population mainly because of cardiac complications and accidents [2, 16, 54, 66].

A US-based Cohort study (N=733) demonstrated that infants with ACH have a 3–6 times greater risk of death than average stature children [54], and the risk of death within the first year of life may be as high as 7.5% [54]. This high rate of sudden infant mortality in patients with ACH is often associated with foramen magnum stenosis and cervicomedullary compression which is prevalent in the infant ACH population (see Section 5.1.2)[2].

5.1.3 Diagnostic

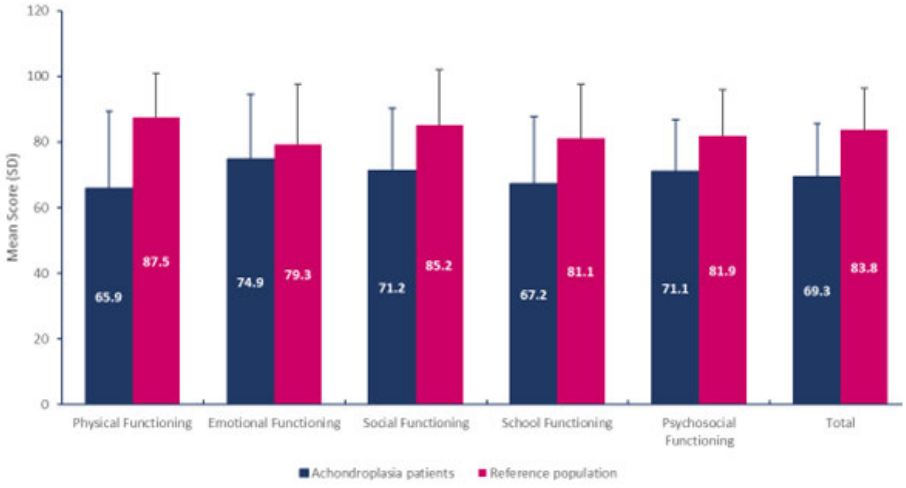
The diagnosis of ACH is usually made on the basis of clinical features from physical and radiographic examinations. The diagnosis is confirmed by a molecular genetic test which shows the main mutation G380R of FGFR3 [67]. Genetic testing allows differentiation of ACH from other less common bone dysplasias, including hypochondroplasia [67].

The majority of patients with ACH are diagnosed in late pregnancy [2]. Indeed, the third trimester ultrasound can identify features of ACH, such as limb shortening, tapered proximal femurs, frontal bump and macrocephaly [2]. The low-dose CT scan performed from 30 weeks of amenorrhea and/or the search for the mutation in amniotic fluid can confirm the diagnosis in antenatal care.

5.1.4 Burden of disease

The clinical manifestations of ACH have a substantial negative impact on patient QoL across many different aspects of life, including physical, social, emotional, and school/work functioning domains (Figure 4). Patients with ACH are often not able to independently carry out activities of daily living (ADL) such as walking longer distances, dressing/bathing, and cooking/housework (Table 3). This has been demonstrated in several studies, using a number of instruments including disease-specific scales and generic measures of QoL (Table 4) [6, 8, 11, 30, 68-74].

Figure 4. Quality of life for ACH patients versus average stature population



PedsQL data . Abbreviations: PedsQL: Pediatric Quality of Life Inventory 4.0; SD: standard deviation.
Source: BioMarin 111-501 Observational Study Report (2020) [9]

Table 3. Impaired activities of daily living among US ACH patients

Activity	Adult ACH patients* reporting loss of ability
Bathe and dress independently	10.7%
Toilet independently	11.3%
Shopping	16.4%
Cook/do housework	15.7%
Walking	2.6%
Walking up a flight of stairs without assistance	14.7%
Walking long distances**	33.3%

**US patients. **Able to walk around the community. Abbreviations: US: United States. Source: Alade et al. (2013)[8]*

Table 4. Key instruments in QoL and ADL

Key instruments	Description
The Pediatric Quality of Life Inventory score (PedsQL™ 4.0)	A generic questionnaire for measuring the quality of life around 4 areas (physical, emotional, social and school functioning) in children and adolescents, presenting a data collection version intended for to children and one destined for parents. Scoring ranges from 0 (worst possible score) to 100 (best possible score). Standard PedsQL reference values for child quality of life are based on a large healthy pediatric sample (N = 9566) aged between 2 and 18 years for self- and parent/carer-reports [75].
The Quality of Life in Short Stature Youth (QoLISSY®)	QoLISSY score is a patient data collection tool specific to young children with short stature, with a collection version intended for children and one for parents, and questions around 7 areas (physical, social, emotional functioning, ability to cope, future, effects on parents, hope). Scores range from 0 (worst score) to 100 (best score).
The Pediatric Functional Independence Measure II (WeeFIM®-II)	WeeFIM® score is a tool for assessing activities of daily living and functional independence, with measurements around 3 domains from the parent/caregiver's perspective (self-care [score range 8 to 56], mobility [score range 8 to 35] and cognition [score range 8 to 35]) and provides a total score between 18 and 126. Higher scores reflect greater functional independence in self-care, mobility and social cognitive skills [76].

It should be noted that due to the early onset of ACH, many patients may experience the 'disability paradox', a phenomenon that causes patients with disabilities to underestimate the impact of their condition compared with healthy populations, due to never having experienced life without the disease in question [77]. This suggests that QoL outcomes are likely to be lower than those reported in the literature.

5.1.4.1 Physical functioning and mobility

Symptoms and complications of ACH, specifically the extreme short stature and disproportionality, severely impact the physical functioning and mobility of patients. The physical QoL scores of ACH patients are lower than those of age- and sex- matched unaffected individuals [69]. Due to disproportionately short upper limbs and restricted joint flexibility, ACH patients are often unable to carry out self-care activities independently (see Table 3) [8, 78].

Short stature, disproportionality, and other orthopedic symptoms of ACH (joint contractures, spinal stenosis, genu varum, and osteoporosis) result in a high proportion of patients struggling to walk long distances or climb the stairs, leading some patients to rely on walking aids [5, 8, 69]. Increased pain (see Section 5.1.2) causes further problems with ambulation which increase with age [5, 8, 56]. Patients with ACH are often not able to overcome physical mobility restrictions by using other means of transportation such as driving (see Section 5.2.1).

5.1.4.2 Social and emotional functioning

Studies have highlighted social barriers as a key cause of reduced QoL among ACH patients, who often have difficulty interacting with others, making and keeping friends, and engaging in sexual relationships [8, 69, 71, 74]. ACH also places a high burden on the psychological and emotional wellbeing of patients, with many experiencing social stigma in their daily lives from a young age [79]. Patients with ACH frequently report low self-esteem, depression, anxiety, and risk factors for suicidal ideation such as social isolation [28, 73, 74]. The high frequency and severity of pain experienced by ACH patients is thought to represent a significant cause of reduced emotional wellbeing among these individuals [69].

5.1.4.3 Societal impact

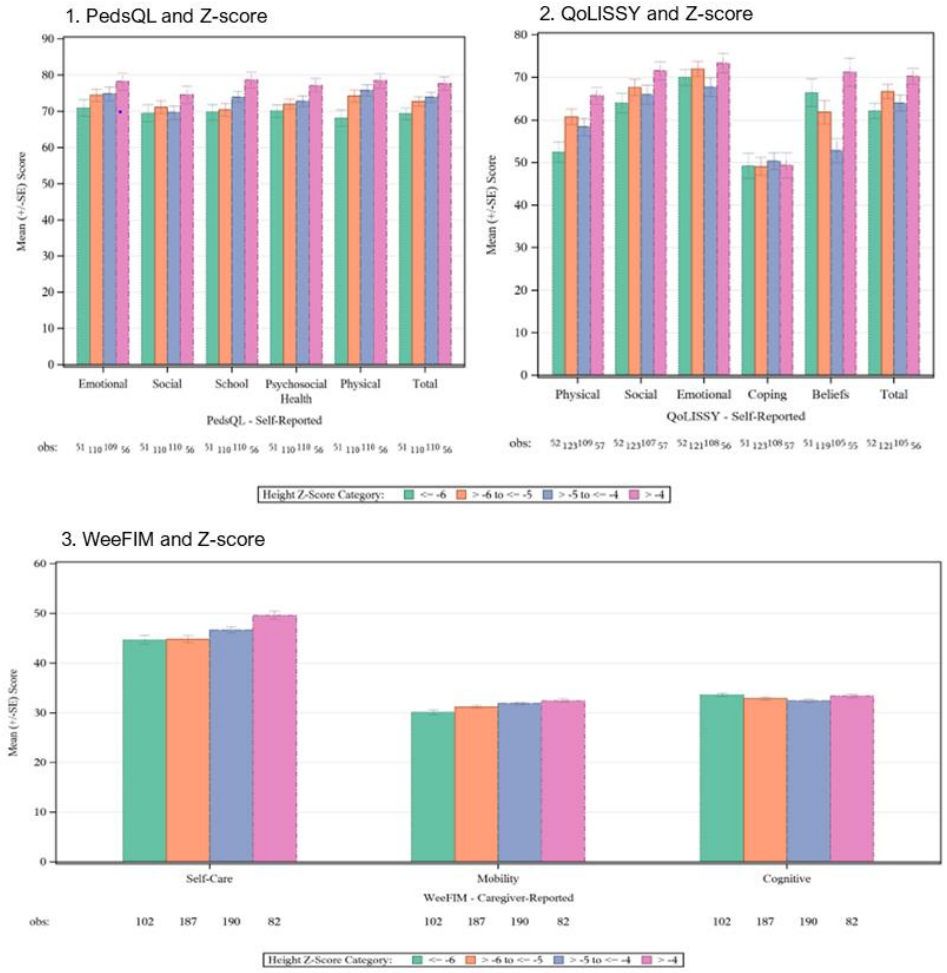
5.1.4.3.1 Education and employment

Children and adolescents with ACH have lower educational attainment compared to unaffected individuals of the same age [10, 71]. Frequent hearing and speech difficulties (see Section 5.1.2) are likely to impact a patient's capacity to listen and communicate in the classroom setting [4, 10], while mobility limitations and social barriers make it challenging for patients with ACH to engage in other typical activities associated with school-life [80, 81]. Students with ACH frequently

experience fatigue after short periods of writing due to restricted joint movement and associated dexterity issues, and severe pain after long periods of sitting [81].

Adult patients with ACH are less likely to be employed than average stature individuals, and may often have a limited range of career choices due to their physical limitations [10]. Patients with ACH may also need to take substantial time off from work due to their symptom burden [9].

Figure 5. Pediatric Quality of Life Inventory Score (1), Quality of Life in Short Statured Youth Score (2), Functional Independence Measure Score (3) and Height Z-Score (Referenced to Average Stature Children)



The height Z-scores were categorized using the subgroup classification from the 111-301 clinical study report, i.e. ≤ −6, > −6 to ≤ −5, > −5 to ≤ −4, > −4 SDS below the average stature.
Source: BioMarin Data on File, The Relationship Between Height Deficit and Health-Related Quality of Life in ACH [37]

In an exploratory analysis of data from the natural history study 111-501, it was found that increasing Z-score was significantly positively correlated with the PedsQL school domain score, which suggests that improved height outcomes may lead to improvements in educational attainment for patients with ACH [10]. Conversely, another exploratory post-hoc analysis of data on height Z-score and HRQoL pooled from studies 111-901, 111-301 and 111-302 (Figure 5) demonstrated that height deficit negatively impacts HRQoL and functional independence in children with ACH, including the PedsQL physical domain, the height-specific QoLISSY physical domain, and the Functional Independence Measure for children (WeeFIM) self-care and mobility domains [36, 37]. With limited exceptions, a trend for a positive impact on HRQoL with reduced height deficit is seen across the individual domains and the total scores for all instruments used, with the height deficit of less than − 4 SDS height Z-score being associated with the highest HRQoL and functional independence scores.

5.1.4.3.2 Caregiver and family quality of life

QoL of individuals caring for patients with ACH is lower than that of the general population [68]. Studies show that caring for an individual with ACH has implications on the physical health, emotional wellbeing and everyday lives of caregivers and families [68, 82, 83].

QoL of an ACH patient's wider family is also negatively impacted. Relatives frequently experience a strain in the family, detrimental effects on family travel/vacations, and limited or adapted family activities to accommodate the child with ACH [14]. There is also an impact on certain acts of daily life (e.g., using the toilet), leading to a certain late dependence on parents/caregivers.

5.1.4.4 Economic impact

5.1.4.4.1 Direct costs

ACH is associated with a financial burden on the healthcare system. From early infancy patients with ACH have higher use of health and social care resources compared with unaffected individuals [9, 10]. To treat and manage the high number of serious and debilitating symptoms and complications (see Section 5.2.1), patients require more frequent consultations with healthcare professionals (HCPs), a high number of invasive surgeries, and the daily administration of several medications to manage complications and pain [9, 10].

In a European natural history study of 184 patients with ACH, HCP visits were reported in 60.8% of patients, with a total of 515 visits across all patients. Appointments with general practitioners (GPs) were reported by 14.5% of patients, occurring at an average rate of 5.7 appointments per 100 person years (PY). Other HCPs frequently visited by patients with ACH included physiotherapists (3.6 appointments per 100 PY) and pediatricians (2.4 appointments per 100 PY) [9]. Patients with ACH also report increased use of medication (see Section 3.1.1) [9, 53].

5.1.4.4.2 Indirect costs

The considerable time required to receive treatments for the symptoms and complications associated with ACH represents a substantial opportunity cost in terms of productivity loss and active participation in other social and economic activities.

ACH has a negative impact on patients' educational attainment and causes substantial challenges in their professional lives (see Section 5.1.4.3); they are less likely to be employed than unaffected individuals, have restricted job options, and are more likely to have to take time off work due to symptom burden [9, 14].

A European natural history study found that 14% of employed patients reported >1 day missed of work in the previous month due to ACH-related events [13]. Further, the performance of ACH patients at work is often impacted by their condition [9]. The reduced ability to work results in income losses which may represent an economic burden to both patients and their families.

5.1.4.4.3 Caregivers, families and wider community costs

ACH also has a negative impact on employment opportunities for caregivers. A study of parents of children with ACH in Spain and the US (N=36) found that up to 14% of parents choose to give up employment entirely in order to care for their child with ACH full-time [14].

In addition to the financial burden of lost income on patients, caregivers, and their families, productivity losses and reduced employment for patients with ACH can have a substantial impact on society. A multicenter study of ACH patients in Europe found that the average (mean) proportion of occupational activity impaired by their condition was 15.4% [9].

5.1.5 Epidemiology

5.1.5.1 ACH in Denmark

According to the approved therapeutic indication, patients with ACH are eligible for treatment from 2 years of age until epiphyseal closure. The birth prevalence of ACH in Europe is estimated to be 3.72/100,000 live births [7], which

considering the average live birth rate in Denmark over the past years (56-63,000 live births per year [84]) would translate into an incidence in Denmark of approximately 2-3 new ACH cases each year, and [redacted] patients in the age span of 2 to 14 years. According to the ACH reference centers in Denmark, approximately 3 new ACH patients are born each year and the number of ACH patients in the 2 to 14 years age span is around [redacted] [7]. The total number of patients in this age span is assumed to be constant, given that approximately the same number of patients will reach and leave the relevant age span each year (Table 5).

Table 5. Incidence and prevalence in the past 5 years in the 2-15 years age span

Year	2024	2025	2026	2027	2028
Incidence in Denmark	3	3	3	3	3
Prevalence in Denmark (age span 2-14 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Global prevalence *					3.72 (/100 000)

Sources: Danish clinical experts [19, 20]; Coi et al [7]

Table 6. Estimated number of patients expected to be treated with vosoritide

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: Danish clinical experts [19, 20]

5.1.5.2 Patient populations relevant for this application

The patient population relevant to this application reflects the approved therapeutic indication in its entirety, i.e. patients with ACH aged 2 years and older whose epiphyses are not closed [1].

The SmPC states that treatment with vosoritide should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses [1]. Based on clinical expert input and consistent with the SmPC recommendation, an anticipated treatment stopping rule in Danish clinical practice would be when the growth plates have closed and growth has stopped as confirmed by individual assessment [19, 20].

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

There is currently no treatment guideline in place for ACH in Denmark.

5.2.1.1 No disease modifying treatments

Besides vosoritide, there is currently no licensed pharmacological treatment available in Denmark which addresses the failure of endochondral bone formation, which is the underlying cause of ACH. Current management of ACH focuses on mitigating symptoms and complications, requiring multiple invasive procedures, prescribed medications, and behavioral/ environmental interventions as well as close supervision. [2]

Some geographies utilise limb lengthening surgery with the aim of increasing height and reach, but these prolonged procedures do not address the underlying cause of disease and only target the long bones, and therefore do not mitigate the impact of the symptoms and complications associated with ACH. Limb lengthening is associated with substantial pain, a considerable risk of severe complications including infections, fractures, and a reduced range of motion, and a QoL burden.[4, 21] As mentioned above and confirmed by consulted clinical experts, limb lengthening surgery is very rarely performed in Denmark and is not recommended by Danish clinical experts [19, 20].

Growth hormone (GH) therapy indicated as treatment option for ACH only in Japan, is not authorized either by EMA or the FDA and has limited evidence to suggest clinical effectiveness. Small increases in growth have been observed, however these were transient and decreased over time. [2]

5.2.1.2 Standard of Care / Symptomatic treatment

ACH patients typically require a number of symptomatic treatments, including both surgical, including invasive procedures, and pharmacological interventions, in order to alleviate the effect of the wide symptoms they suffer [2, 9, 10]. For example, a US multicenter natural history study found that of 1,374 patients, 79.6% had undergone at least one prior ACH-related surgery and collectively the cohort had undergone 4,552 surgeries (average 3.3 per patient) [85]. Similarly, a multicenter study in Europe found that of 186 patients, 72% had undergone at least one surgical procedure, corresponding to a total of 513 surgeries across all patients (average 2.8 per patient) [9].

A range of prescribed medications are frequently used by patients with ACH to manage their symptoms. A multicenter study of adult and pediatric ACH patients in Europe found that >70% of 186 patients had taken at least one prior medication [9].

5.2.1.3 Environmental and behavioral interventions

In addition to surgery and prescribed medications, patients and their families are often recommended to make environmental and behavioral changes to adapt to the needs of the ACH patient [86-88]. For example, parents and caregivers are advised to use straight back baby furniture and to avoid the use of slings or baby seats which allow for curvature of the child's spine [86, 89], to reduce the risk of spinal complications, such as thoracolumbar kyphosis. These recommendations are also advised when the patient begins attending school; chairs should be adapted, with cushioning to support the back and prevent kyphosis and a footrest or step to prevent legs from dangling and causing numbness [87, 90]. Other furniture adaptations which are frequently required including the reduced height of door and cupboard handles in the home, and a stool to allow access to the toilet [87]. To overcome the impact of short limbs and reduced reach on the ADL of ACH patients, reach extenders may be used (for example in toileting or other personal hygiene tasks) [87]. Adaptations may also be required for driving including pedal extenders [87]. Adaptations to vehicles must be approved by the government and the support a patient receives may by limited if height thresholds are applied to disability status (in Germany, a height threshold of 140 cm is used) [91].

5.2.2 Choice of comparator(s)

Vosoritide is the first and only licensed pharmacotherapeutic treatment that directly addresses the underlying cause of ACH. It is an innovative treatment with no equivalent existing comparator, and there are no other alternative pharmacotherapeutic treatments available. Current standard of care is focused on managing the range of symptoms and complications that each patient presents with.

Lacking a relevant comparator, the evaluation of **the efficacy and safety of vosoritide is in this dossier presented in comparison with placebo/ ACH natural history**. The effect on the Danish landscape will be compared with and without the introduction of vosoritide.

5.2.3 Description of the comparator(s)

Not relevant; there are no other alternative pharmacotherapeutic treatments available, and the only relevant comparator is best supportive care as described by ACH natural history data.

5.3 The intervention

5.3.1 Dosing

It is important to initiate treatment in children as young as possible.

The volume of vosoritide to be administered at the recommended dose is based on the patient's weight and the vosoritide concentration (see Table 7 below). The usual dose is 15 µg/kg body weight. For practicality reasons and to account for weight-related pharmacokinetics changes (see section 5.2 of SmPC), the dosing presented in Table 7 is recommended [1].

Table 7. Single dose volumes by body weight

Body weight (kg)	Vosoritide 0.4 mg solvent (water for injections): 0.5 mL concentration: 0.8 mg/mL	Vosoritide 0.56 mg solvent (water for injections): 0.7 mL concentration: 0.8 mg/mL	Vosoritide 1.2 mg solvent (water for injections): 0.6 mL concentration: 2 mg/mL
	Daily injection volume (mL)		
10-11	0.30 mL		
12-16		0.35 mL	
17-21		0.40 mL	
22-32		0.50 mL	
33-43			0.25 mL
44-59			0.30 mL
60-89			0.35 mL
≥ 90			0.40 mL

5.3.2 Method of administration

Vosoritide is administered as a once daily (QD) subcutaneous injection. It can be administered at home by caregivers under the direction of a healthcare provider [1].

5.3.3 Treatment duration/criteria for treatment discontinuation

The SmPC states that treatment with vosoritide should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses [1].

Based on clinical expert input [19, 20], an anticipated treatment stopping rule in Danish clinical practice in line with the SmPC recommendation would be according to individual assessment, when, the growth plates have closed, and growth has stopped.

5.3.4 Should the pharmaceutical be administered with other medicines?

No [1].

5.3.5 Necessary monitoring, during administration, during the treatment period, and after the end of treatment

Patients should be monitored and assessed regularly every 3-6 months to check body weight, growth and physical development. Dose should be adjusted according to the patient's body weight [1].

5.3.6 Need for diagnostics or other tests (i.e., companion diagnostics)

No.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Appendix A reports the relevant findings of a systematic literature review (SLR) carried out to identify treatment outcomes, including clinical efficacy and safety of vosoritide for the treatment of ACH.

The original searches for the de novo SLR were run in September 2020; updates were subsequently performed in June 2021 (first update) and July 2022 (second update), the results of the two SLR updates have been integrated into one SLR hereafter referred to as broader SLR [92]. A recent SLR initiated by BioMarin in 2021 was used as a basis for the DMC literature search. This broad literature review had a broader scope than the literature search aimed for DMC (DMC literature search) and also included a search for studies of other potential therapies of ACH such as growth hormone

therapy and limb lengthening surgery that could be of potential relevance on other markets. Since these treatments are not used in Danish clinical practice, any articles on other interventions than vosoritide were considered irrelevant for the purpose of the current DMC application and were therefore excluded from the DMC literature search.

6.2 List of relevant studies

The SLR identified 2,440 unique records, of which 207 were selected for full text review.

After the selection process, a total of 25 citations describing nine studies (Table 8) were included in the DMC application.

Table 8. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
C-Type Natriuretic Peptide Analogue Therapy in Children with ACH. Savarirayan, R., et al., N Engl J Med, 2019 [27]	111-202	NCT02055157	January 13, 2014-October 2, 2017 Completed	Vosoritide efficacy and safety
Vosoritide for Children with ACH: A 60-month update from an ongoing Phase 2 clinical trial. Hoover-Fong J., et al. Presented at the ACMG Annual Clinical Genetics Meeting: April 13–16, 2021 [93]	111-205	NCT02724228	January 26, 2016-October 2022/February 2028?	Vosoritide vs NH
A randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia. Poster presented at the Endocrine Society's 2022 Annual Meeting, June 11-14, 2022, Atlanta, GA, Savarirayan et al., 2022 [94]	111-206	NCT03583697	May 23, 2018-January 26, 2022 Completed	Vosoritide vs Placebo
An Extension Study to Evaluate Safety and Efficacy of BMN 111 in Children with ACH (phase 2) No publication yet	111-208	NCT03989947	June 12, 2019-December 2026	Vosoritide efficacy and safety
Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with ACH at risk of requiring cervicomedullary decompression surgery. Savarirayan, R., et al., Sci Prog. 2021 [95]	111-209	NCT04554940	October 10, 2020-December 2026	Vosoritide efficacy and safety
Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. Savarirayan, R., et al., Lancet, 2020. 396(10252): p. 684-692. [22]	111-301	NCT03197766	December 12, 2016-October 30, 2019 Completed	Vosoritide vs Placebo
Safe and persistent growth-promoting effects of vosoritide in children with ACH: 2-year results from an open-label, phase 3 extension study. Savarirayan R., et al., Genetics in Medicine, 2021 [96]	111-302	NCT03424018	December 12, 2017-December 2024	Vosoritide vs NH
Lifetime impact of achondroplasia study in Europe (LIAISE): findings from a multinational observational study.	111-501	NCT03449368	December 17, 2017-April 29, 2020 Completed	Vosoritide vs NH

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Maghnie M, et al., Orphanet Journal of Rare Diseases, 2023 [97]				
Growth parameters in children with achondroplasia: A 7-year, prospective, multinational, observational study. Savarirayan R., et al., Genetics in Medicine, 2022 [98]	111-901	NCT01603095	April 2012 – February 2021 Completed	Vosoritide vs NH

Abbreviations: NH: Natural History

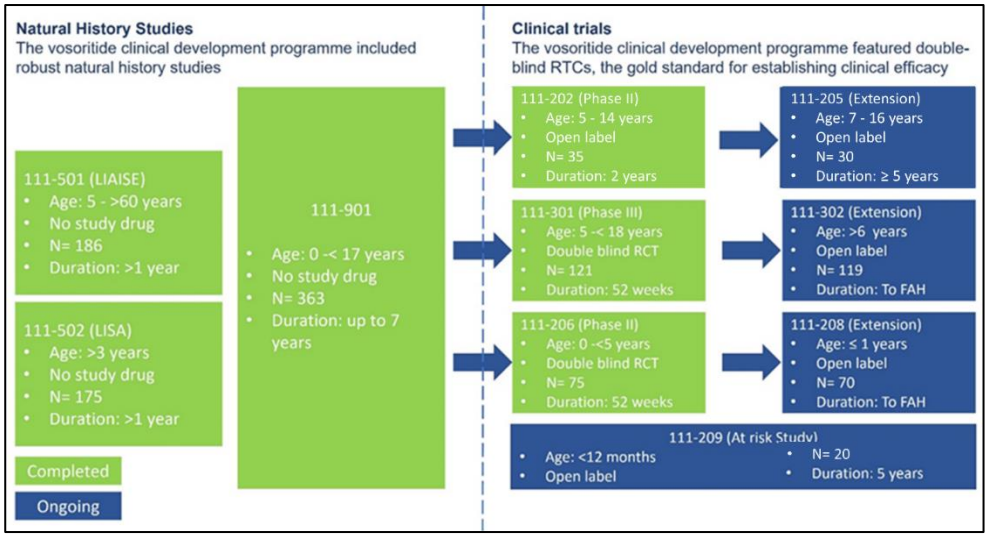
7. Efficacy and safety of vosoritide compared to placebo for children with ACH

7.1 Overview of clinical development program and relevant studies

Despite the rarity of ACH, the efficacy and safety of vosoritide has been investigated within an extensive and robust clinical development program including a relatively high number of patients, which is uncommon in the field of rare diseases. The program includes Phase II and Phase III placebo-controlled, randomized controlled trials (RCTs) and extension studies, as well as non-interventional natural history studies, conducted in patients aged 0–18 years. Available results in patients aged 2–18 years show that vosoritide consistently achieved clinically meaningful and sustained height outcomes.

The clinical development program for vosoritide is shown in Figure 6. Detailed study characteristics for studies included in this assessment are found in Appendix B.

Figure 6. Overview of clinical study program for vosoritide



Natural History Studies:

- **111-901** [99], performed by BioMarin, to characterize growth data in pediatric patients with ACH (defined as children or infants <2 years of age) eligible for inclusion in the following studies successively conducted by BioMarin. This study also established the historical control Cohort, used as a comparator for Phase II and III studies 111-205 and 111-302.

- Study **111-501** [100] (LIAISE): a multinational observational study of medical care, QoL, costs, and socioeconomic, clinical, and psychosocial management of patients with ACH in Europe
- Study **111-502** [101] (LISA): an ongoing, multinational, epidemiological, observational, retrospective study of the burden of disease in ACH patients aged 3 years and older, conducted at four study sites in three Latin American countries (Brazil, Argentina, and Colombia) to investigate the QoL, HCRU, and clinical, socio-economic and psychological burden in ACH patients versus an average stature population [101]. Since there are currently no results available for this study [101], it is not included in the current assessment and no further details about the study are provided.

Phase II studies:

- **111-202** [102], dose finding in patients aged 5 to 14 years, and its extension study: **111-205** [103]
- **111-206** [104], a multicentered, randomized, double-blind, controlled, versus placebo study in patients aged 0 to 5 years, and its extension study: **111-208** [105]
- **111-209** [106], a "patients at risk" study carried out in infants aged 0 to ≤12 months with ACH at high risk of undergoing cervicomedullary decompression surgery.

Phase III studies:

- **111-301** [107], a multicentered, randomized, double-blind, in parallel groups, comparative versus placebo study in patients aged 5 to 18 years, and its extension study: **111-302** [108]

Together, these studies provide evidence in patients aged 0–18 years, which covers the age range specified in vosoritide's license; patients with ACH 2 years of age and older whose epiphyses are not closed.

7.2 Efficacy and safety – results per study

7.2.1 Clinical Studies Phase III

7.2.1.1 Study 111-301

111-301 is a Phase III randomized, placebo-controlled, double-blind multicenter trial to evaluate the effect of vosoritide on growth, QoL and incidence of AEs in patients treated with vosoritide compared with control patients in the placebo group in patients with ACH [109].

A total of 121 patients were enrolled into 111-301; 61 patients were randomized to receive placebo and 60 patients to receive vosoritide 15 µg/kg. Baseline characteristics for included patients are presented in Appendix C Section 14.1.3.

By Week 52, all except two patients had completed the trial. Both patients who withdrew from the trial were in the vosoritide treatment group; one discontinued drug administration due to an AE (anxiety about injections; n=1 [1.7%]) and the other due to a patient request (pain during injections; n=1 [1.7%]). Both patients went on to withdraw from the trial after treatment discontinuation [109]. Patient disposition for patients in 111-301 is presented in Figure 7.

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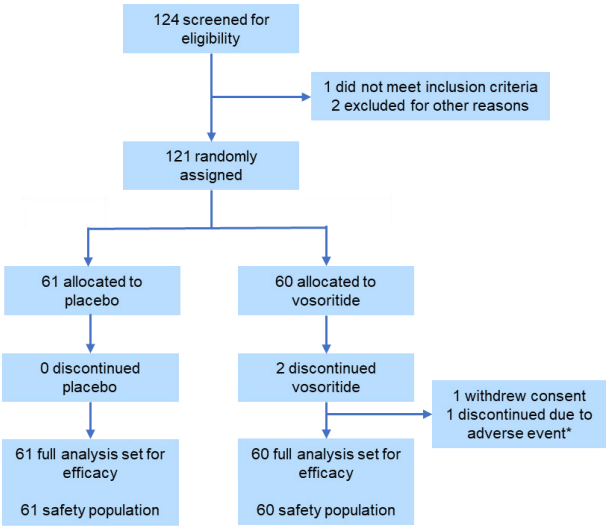
Figure 7. Patient disposition for 111-301 (full analysis set)



**Injection anxiety.*
Source: Savarirayan, 2020 [22]

Detailed study characteristics is found in Appendix B and baseline characteristics of patients is found in Appendix C. Detailed study results are presented in Appendix D.

7.2.1.1.1 Key clinical findings

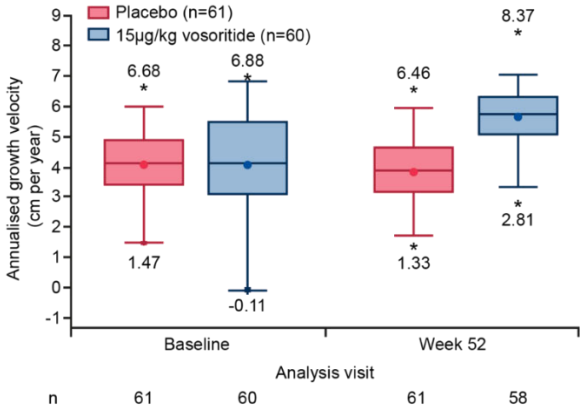
Detailed study results are presented in Appendix D.

Annualized growth velocity

The primary outcome was the difference between the vosoritide group and the placebo group in the mean change from baseline in AGV at the 52-week time point.

At baseline, the mean (SD) AGV was similar between the two treatment groups, and by Week 52, AGV was significantly improved with vosoritide compared with placebo (least-squares mean change from baseline: vosoritide 1.71 cm/year (95% CI 1.40 to 2.01), placebo 0.13 cm/year (95% CI −0.18 to 0.45); P<0.0001) [109] (Figure 8, Table 9). The increase in AGV observed in vosoritide-treated patients represents a restoration of a substantial proportion of the AGV deficit compared with average stature children [22].

Figure 8. Box and whisker plot of annualised growth velocity at baseline and 52 weeks by treatment arm for patients in 111-301



**Outliers. Source: Savarirayan, 2020 [22]*

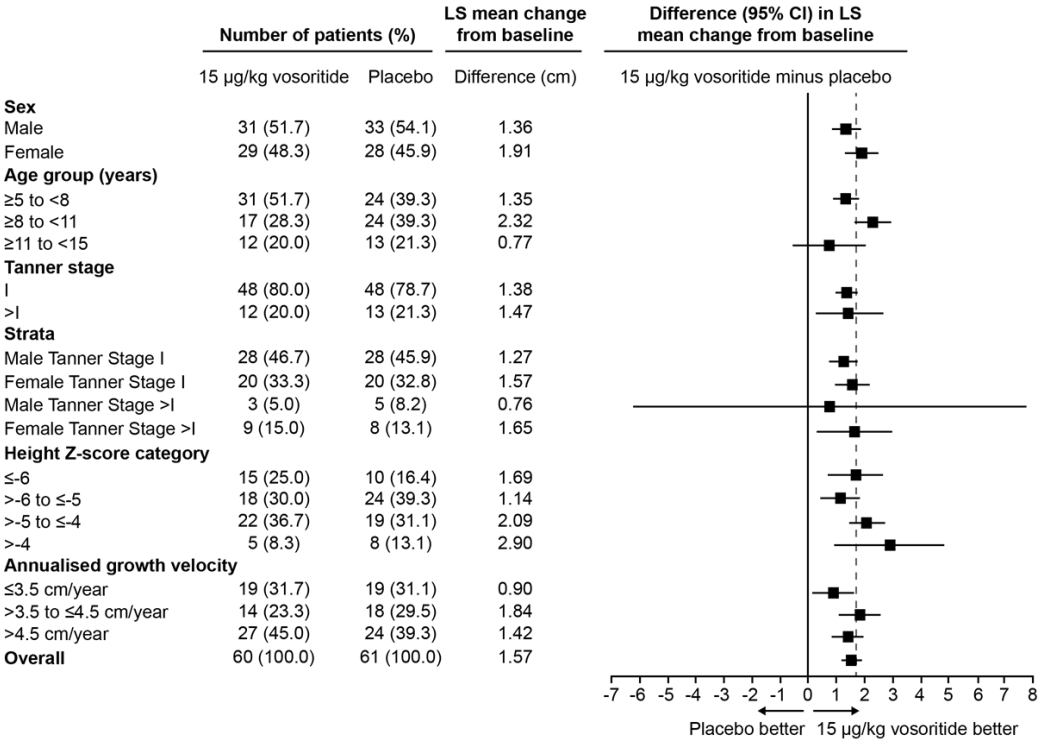
Table 9. Annualised growth velocity for vosoritide and placebo

Annualised growth velocity (cm/year) (Mean ± SD)						
Placebo (N=61)			Vosoritide 15ug/kg daily (N=60[c])			Vosoritide vs. placebo
Baseline	Week 52	Change	Baseline	Wek 52	Change	LS Mean difference in changes (95% CI)
4.06 ± 1.20	3.94 ± 1.07	-0.12 ± 1.74	4.26 ± 1.53	5.61 ± 1.05	1.35 ± 1.71	1.57[a] (1.22, 1.93) (p=< 0.0001[b])

AGV, annualised growth velocity; 95% CI, 95% confidence interval; LS, least-square; SD, standard deviation.
[a] Difference is 15 µg/kg Voxzogo minus placebo.
[b] Two-sided p-value.
[c] Two patients in the Voxzogo group discontinued from the study before Week 52. The values for these 2 patients were imputed for this analysis.
LS mean estimated from the ANCOVA (analysis of covariance) model adjusted for baseline differences between the two arms, analysis of covariance. Source: SmPC [1]

Furthermore, subgroup analyses showed that vosoritide improved AGV at Week 52 consistently across all pre-defined subgroups (sex, age group, Tanner stage baseline height Z-score, baseline AGV) with overlapping 95% CIs across all subgroups [22] (Figure 9). In the Tanner stage >I male subgroup, the treatment effect estimate was in favor of vosoritide, but the confidence intervals were wide and included zero. However, there were only 8 subjects in this subgroup (respectively, 3 and 5 subjects in the vosoritide group and the placebo group) [109].

Figure 9. LS mean change from baseline in AGV at Week 52 of 111-301 by patient subgroup



Abbreviations: AGV: annualised growth velocity; CI: confidence interval; LS: least square.
The vertical dotted line represents the change from baseline difference of 1.75 cm/year for which the study was powered.
Source: Savarirayan 2020.[22]

Height Z-score

At baseline, the mean (SD) height Z-scores were similar between treatment groups. By Week 52, the LS mean change from baseline in height Z-score was significantly greater in patients in the vosoritide treatment group compared to those in the placebo group. [22]

Furthermore, subgroup analyses showed that vosoritide improved Z-score at Week 52 consistently across the majority of pre-defined subgroups (sex, age group, baseline height Z-score, baseline AGV) with overlapping 95% CIs. For Tanner Stage >I there was no difference in height Z-score between the vosoritide and placebo treatment arms.[30] This was driven by the data for females Tanner Stage >I and is in contrast to the clear treatment effect in favour of vosoritide observed on change in AGV in this subgroup [109].

Standing and sitting height

Patients with ACH have near-normal trunk length, but experience substantial impairments to bone development in the limbs.[110] As such, sitting/standing height ratios (which signify the proportion of total height represented by the upper body) in ACH patients are substantially greater than ratios for average stature individuals.[110] ACHIn 111-301, baseline mean standing and sitting heights were slightly lower in the vosoritide group compared to placebo, attributable to the vosoritide group having slightly younger patients (more patients aged 5–8 years old). By Week 52, patients treated with vosoritide showed a greater change from baseline in both sitting [redacted] and standing (5.59 (SD 1.06) versus 3.93 (SD 1.08) cm) heights, and the LS mean differences in change between treatment groups were significant and in favour of vosoritide 1.57 (1.21, 1.93); p=0.0001 and [redacted], for standing and sitting height respectively [109].

Individual standing height data plotted over time by treatment group and sex for average stature age-sex specific reference data and ACH age-sex specific reference data are shown in Figure 10.

Figure 10. Standing height trajectories for patients in 111-301

Upper to Lower Body Segment ratio

Baseline upper to lower body segment ratios were similar between the treatment groups. LS mean changes from baseline to Week 52 in upper to lower segment body corresponded to a difference in LS mean change from baseline of

−0.01 (95% CI: −0.05, 0.02; P<0.5060), indicating that there was no difference between treatment groups. [109] Importantly, there was no worsening in upper to lower body segment ratio which is clinically relevant as it indicates that the observed increase in growth is occurring proportionally in both the spine and the lower limbs. [22]

Quality of Life and Activities of Daily Living

PedsQL: At baseline, caregiver- and self-reported PedsQL scores were similar in both treatment groups. At Week 52, no difference was observed in change from baseline between the vosoritide and placebo groups in any of the PedsQL domains for caregiver- or self-reported scores. [22]

QoLISSY: At baseline, caregiver reported QoLISSY scores were generally similar in both treatment groups. For self-report QoLISSY scores at baseline, some differences were noted in physical, coping, and belief scores between treatment groups [109]. Physical and belief scores were numerically lower (indicating worse QoL), whilst the coping score was numerically higher (indicating better QoL) in the vosoritide group compared to placebo group [109]. Caregiver-reported QoLISSY scores tended to be lower than self-reported scores; this trend was noted in most domains. [22]

At Week 52, no difference was observed in change from baseline between the vosoritide and placebo groups in any of the caregiver-reported QoLISSY domains. For self-reported QoLISSY scores, no clear difference was observed between the vosoritide and placebo groups. However, for belief score, a small numerical improvement was observed in the vosoritide group compared to placebo. Of note, values differed in this domain at baseline between the two treatment groups. [22]

WeeFIM: At baseline, WeeFIM scores were similar in both treatment groups, [109]. At Week 52, there was no difference observed in the change from baseline between the vosoritide and placebo groups in any of the domains. [22]

Detailed results are presented in Appendix D.

Safety and tolerability

Overall, similarly high proportion of patients in both placebo (60/61; 98%) and vosoritide (59/60; 98.3%) groups experienced at least 1 AE during the trial, and 10 patients in each group experienced AEs that led to dose interruption. In the vosoritide group, 1 patient experienced an AE (anxiety to injections) that led to permanent discontinuation of trial drug. The majority of AEs reported in the trial were Grade 1 (mild) or Grade 2 in both groups. Grade 3 AEs were reported less frequently, and no Grade 4 AEs or deaths were reported. Treatment-related AEs were reported in 51/61 (83.6%) patients in the placebo group and 53/60 (88.3%) patients in the vosoritide group, none of these were SAEs or Grade 3 or higher AEs [22, 109].

SAEs were reported more frequently in the placebo group than in the vosoritide group. No SAEs were attributed to the trial drug by the investigators, and none led to discontinuation of trial drug or the trial [109].

An overview of the overall incidence of AEs among the safety population is presented Appendix E.

Bone metabolism biomarkers

In addition, bone morphology was analysed through X-ray and dual energy X-ray absorptiometry. Despite vosoritide leading to improved height, there were no significant changes in either bone mineral content or density and bone age progression in patients receiving vosoritide.[22] This is suggestive of normal skeletal maturity [30] and indicates that vosoritide does not reduce the total duration of the growth period.

7.2.1.2 Study 111-302

111-302 is an ongoing Phase III open-label, multicentre long-term extension trial to evaluate the effect of vosoritide on growth velocity in children with ACH who completed 1 year of vosoritide or placebo treatment in the parent trial 111-301.[33] Subjects who completed 1 year of vosoritide or placebo treatment in study 111-301 were eligible to enrol in the 111-302 extension study and continue to receive vosoritide 15 µg/kg daily, (vos/vos group, if randomised to

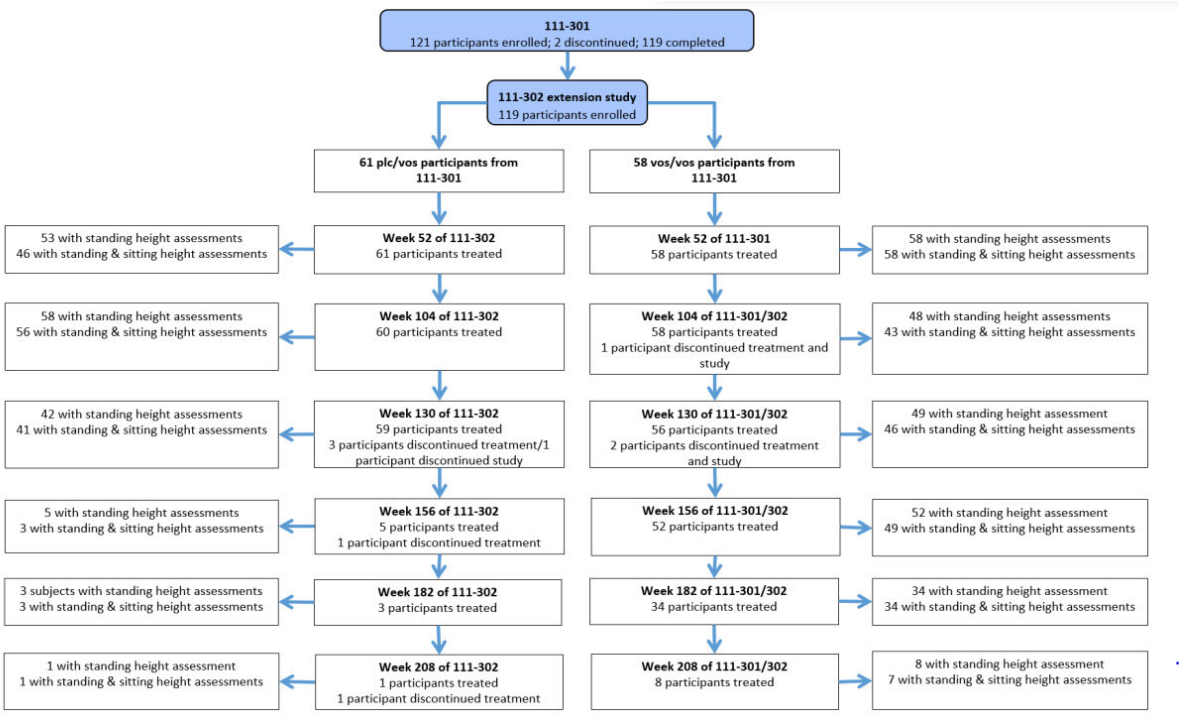
vosoritide in study 111-301), or start vosoritide 15 µg/kg daily for the first time (plc/vos group, if randomised to placebo in study 111-301). This long-term extension study allows for assessment of the effect of daily vosoritide administration on AGV, growth (height Z-score), and body proportions (upper to lower body segment ratio) in subjects treated with vosoritide, as well as further characterization of its safety and tolerability in children with ACH.

In particular, the efficacy analyses in study 111-302 are presented focusing on:

- Vos/vos group – whether treatment efficacy observed at Week 52 in study 111-301 is maintained in study 111-302 at Week 104 (second year of treatment) and trough 130 weeks of continuous vosoritide treatment
- Plc/vos group – whether treatment efficacy after switching from placebo to vosoritide treatment at Week 52 in study 111-302 is similar to the efficacy observed at Week 52 in the vos/vos group in study 111-301.

Patient disposition for patients in 111-302 is presented in Figure 11. A total of 119 patients were enrolled in 111-302, having completed the parent trial 111-301. A total of 8 participants overall discontinued from treatment (4 of whom also discontinued the study). [33]

Figure 11. Patient disposition study 111-302



Vos/vos, 111-301 vosoritide group; plc/vos, placebogroup.
Visits are the CRF planned visit Height assessments were based on analysis window visits.
Source: BioMarin Efficacy Update Report 111-302, 2023 [111]

Detailed study characteristics is found in Appendix B and baseline characteristics of patients is found in Appendix C. Detailed study results are presented in Appendix D.

7.2.1.2.1 Key clinical findings

The current efficacy analyses are based on data collected from the first dose of vosoritide, either from the start of Study 111-301 (vosoritide/vosoritide (vos/vos) group) or from the start of 111-302 (placebo/vosoritide (plc/vos) group). Baseline is defined as the last assessment before the first dose of vosoritide treatment. Results from the most recent Efficacy Update Report (data cut-off date of 25 February 2022) are included here and presents change from baseline in AGV, height Z-score (average stature reference), height Z-score (ACH reference), standing height, and upper to lower body ratio up to the data cut-off [111, 112]. The evaluation of efficacy over time was assessed in the Full Analysis Set

(FAS) population. The FAS was defined according to the intention-to-treat principle and included all enrolled subjects with a signed informed consent for 111-302. The FAS was used to present the baseline characteristics and efficacy data.

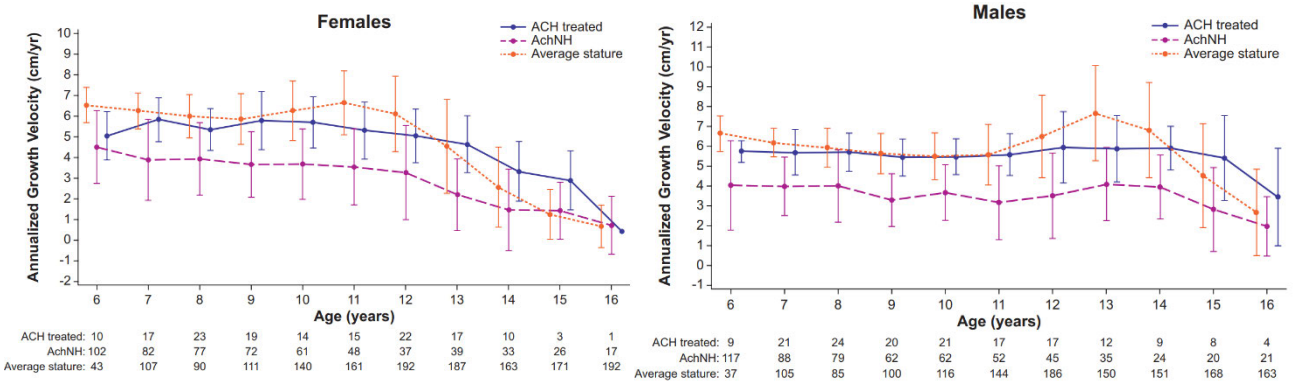
By the cut-off date February 25, 2022, 52 patients in the vos/vos treatment arm had completed 156 weeks in the extension study 111-302 (receiving 15 µg/kg vosoritide for 208 weeks in total) and 58 patients in the plc/vos treatment arm had completed 130 weeks in 111-302 (receiving 15 µg/kg vosoritide for 130 weeks in total) [111].

Annualized growth velocity

The improvement in AGV observed in children treated with vosoritide in 111-301 was maintained for the vos/vos subjects in 111-302 with a mean (SD) 12-month interval AGV for the first four years [redacted] For participants in the plc/vos group, the mean (SD) 12-month interval AGV for first three years was [redacted] Vos/vos patients demonstrated a durable improvement in AGV over four years of vosoritide treatment [111].

As illustrated in Figure 12, AGV of patients treated with vosoritide is consistently higher compared to age-matched untreated children. The difference in the mean integer AGVs across each integer age (6-16 yrs) between treated and untreated was 1.55 (0.78) cm/year in females and 1.98 cm/y in males [112].

Figure 12. Mean integer AGVs across each integer age (6-16 years)



AchNH (Ach Natural History) reference derived from CLARITY (Hoover-Fong J et al. Orphanet J Rare Dis. 2021) [113]. Average stature reference is non-African American data from Kelly A et al. J Clin Endocrinol Metab. 2014 [114]
Source: Poster presented at the 2023 ACMG Annual Clinical Genetics Meeting, March 14-18 2023 - Hoover-Fong et al., 2023 [112]

In the vos/vos group the mean (standard deviation [SD]) cumulative AGV improved from [redacted] cm/year at baseline (n=58) to [redacted] cm/year at week 182 (n=34). For the plc/vos group, the mean (SD) cumulative AGV improved from [redacted] cm/year at baseline (n=61) to [redacted] cm/year at Week 130 (n=42) which demonstrates treatment effect in participants who switched from placebo to vosoritide after 1 year of receiving placebo in 111-301 [111].

Height Z-score

In the vos/vos group the mean (SD) height Z-score improved from [redacted] SDS at baseline (n=58), with change from baseline of [redacted] SDS at Week 104 (n=48) and [redacted] SDS at Week 156 (n=52). In participants who continued vosoritide treatment, the improvement in height Z-score was maintained at Week 182 (n=34) with a change from baseline of [redacted] SDS. For the plc/vos group mean (SD) height Z-score improved from [redacted] SDS at baseline (n=61) with change from baseline of [redacted] SDS at Week 104 (n=58) and [redacted] SDS at Week 130 (n=42) Figure 13 [111].

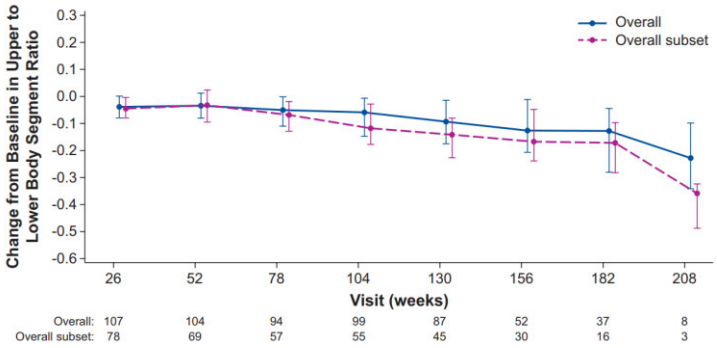
Figure 13. Mean (SD) height Z-score over time in 111-302

[redacted]

Upper to lower body segment ratio

At the latest data cut off, no worsening in upper to lower body segment ratio over time was observed in both treatment groups [111]). In the vos/vos group, the mean (SD) upper to lower body segment ratio was [redacted] at baseline (n=58), with change from baseline of [redacted] At Week 104 (n=43) there is an erroneous data point that impacts the mean and hence the median change of [redacted] reflects more accurately the change from baseline at this time point. In participants who continued vosoritide treatment, the effect was sustained up to Week 182 (n=34) with a change from baseline in the upper to lower body segment ratio of [redacted]. In plc/vos group, the mean (SD) upper to lower body segment ratio was [redacted] at baseline (n=61) with change from baseline of [redacted] after 104 weeks (n=56). For the plc/vos group, the effect improvement in upper to lower body segment ratio was consistent with that observed in the vos/vos group. In participants who continued to receive vosoritide, the effect was maintained at Week 130 (n=41), with a change from baseline of [redacted] [111].

Figure 14. Change in upper to lower body segment ratio (median, Q1Q3) in the overall population and in subset of children under 11(f)/12(m) years old



Proportionality changes up to ~age 11 (girls) / 12 (boys). Older children excluded from analysis given any treatment is unlikely to impact proportionality beyond this point.
Source: Poster presented at the 2023 ACMG Annual Clinical Genetics Meeting, March 14-18 2023 - Hoover-Fong et al., 2023 [112]

2-year comparative analysis

Comparative analyses were conducted to assess the height gain, z-score and upper to lower body segment ratio for all vos/vos participants after two years on active treatment with a height assessment at week 104 (n = 52) versus the participants in the plc/vos arm with two years of untreated follow up considering the placebo period and an additional year from the observational study prior to start of the randomized controlled study (n = 38). By directly comparing the treated group to the untreated group, the observed change in height was similar in the first year of treatment, 1.73 cm, as in the second year of treatment, 1.79 cm. The additional height gain over the two-year treatment period was 3.52 cm more than the untreated children (Table 10) [96].

The LS-mean difference in AGV (95% CI) was 3.34 cm (2.76, 3.93). the difference in LS-mean change in height Z-score (95% CI) was +0.44 (0.25, 0.63) at week 104 [96] and the difference in LS-mean change from baseline in upper-to-lower body segment ratio (95% CI) was −0.05 (−0.09, −0.01) at week 104 representing a greater decrease in the body ratio in the vosoritide treated versus the untreated participants (Figure 15) [96].

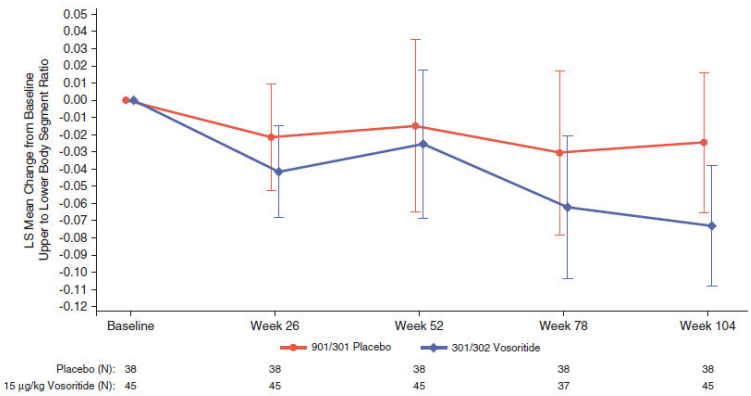
The comparative analyses at two years were performed using the same analysis of covariance (ANCOVA) model, which adjusted for covariates [redacted] as prespecified for the primary and key secondary analyses of the randomized placebo-controlled study 111-301 [109].

Table 10. AGV for patients over two years

Mean (SD) change in AGV, cm/year	Untreated (N=38*)	Vosoritide (N=52**)
52 weeks	3.96 (0.92)	5.69 (0.97)
104 weeks	3.82 (0.99)	5.61 (1.09)
Difference in AGV between treatment groups (95% CI); p-value* **		
52 weeks	1.73 (1.33, 2.14); p<0.0001	
104 weeks	1.79 (1.35, 2.24); p<0.0001	

**38 participants were enrolled in the run-in study more than 12 months and were at least 5 years of age at that point of time in advance of randomisation and therefore contribute at least 2 years of evaluation of height in the absence of treatment.*
***Data from 6 patients were unavailable due to patient withdrawals during Year 2 (n=2) and due to restrictions in study conduct because of Covid-19 (n=4). The patients whose data are not available due to COVID-19 are still on treatment.*
****p-value for unadjusted treatment effect.*
Abbreviations: AGV: annualised growth velocity; CI: confidence interval; SD: standard deviation.
Source: BioMarin 2020 [30] Savarirayan R. et al (2021) [96]

Figure 15. Line plot showing analysis of covariance (ANCOVA) LS mean change from baseline with 95% CI for upper-to lower body segment ratio in 6-month intervals for a total of 24 months and displayed by treatment arm.



Source: Savarirayan R. et al (2021) [96]

Key safety results

No new adverse effects of vosoritide treatment at 15 µg/kg/day were detected with three years of continuous daily, subcutaneous treatment. Most subjects experienced at least 1 AE during the study, 116/119 (97,5%) subjects. Most adverse events were mild, and transient injection site reactions continue to remain the most common AE [122]. No serious adverse events were attributed to vosoritide. No subject experienced an AE that led to discontinuation of study drug or study. AE of CTCAE Grade ≤3 were reported by 12/119 (10.1%) subjects. SAEs were reported in 14/119 (11.8%) subjects. The SAEs reported were generally attributed to underlying ACH, one treatment related SAE of genu valgum, attributed to growth and underlying joint damage due to ACH [122].

7.2.1.3 Conclusions 111-301 and extension study 111-302

The Phase III study 111-301 achieved its main objective, with a difference in the variation in the annualized growth rate between the two groups at 52 weeks compared to the baseline, statistically significant in favor of the vosoritide group, i.e., 1.57 cm/year (95% CI: [1.22; 1.93], p <0.0001). [22]

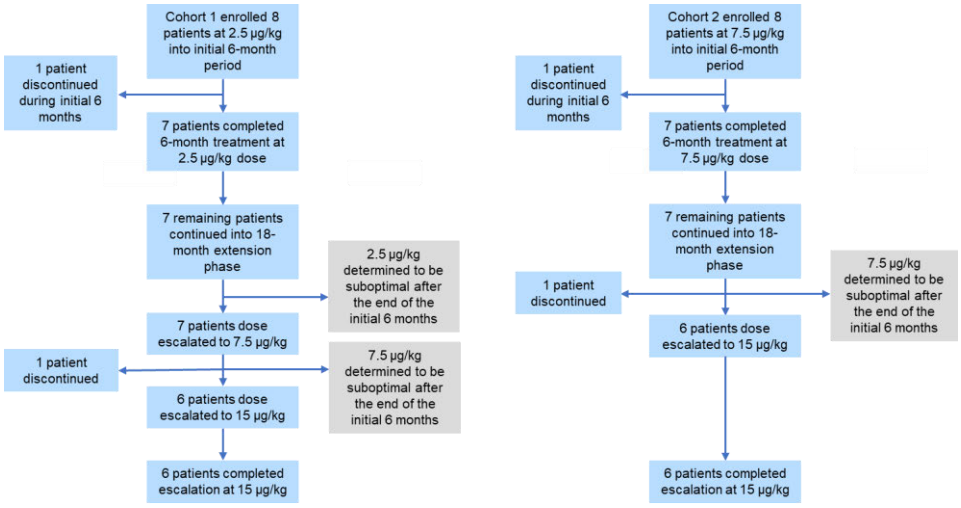
The results presented here for the extension study 111-302 are interim results and confirm a positive effect on growth with vosoritide in children with achondroplasia aged 5-18 years. Patients in the vos/vos arm demonstrated a durable improvement in AGV over three years of vosoritide treatment, resulting in continued increases to height Z-score and a positive trend in body proportion ratios. Subjects switching from placebo in 111-301 to vosoritide for the first time in study 111-302, experienced an improvement in height Z-score over the initial treatment period. The magnitude of improvement in height Z-score after initiation of vosoritide treatment was similar between subjects in plc/vos group and vos/vos group. Improvement in the upper to lower body segment ratio were also observed.

7.2.2 Clinical Studies Phase II

7.2.2.1 Study 111-202

111-202 is a Phase II open-label, sequential Cohort dose-escalation trial of vosoritide in ACH patients aged 5–14 years. A total of 35 patients were enrolled into 111-202; eight patients were enrolled into each of Cohorts 1 and 2, ten patients were enrolled into Cohort 3 and nine patients into Cohort 4.[31] During the extension period, one patient discontinued from each of Cohorts 1 and 2, bringing the total number of patients who completed the two-year study to 30. [31] Further, 12 patients across Cohorts 1 and 2 were switched to vosoritide 15 µg/kg during the extension phase of the trial (see Figure 16).[31]

Figure 16. Patient disposition for 111-202



Source: BioMarin 2018(A) Clinical Study Report: 111-202.[31]

Detailed study characteristics is found in Appendix B and baseline characteristics of patients is found in Appendix C. Detailed study results are presented in Appendix D.

7.2.2.1.1 Key clinical findings

Detailed study results are presented in Appendix D.

Annualized growth velocity

By Month 6, a positive, dose-dependent change in mean (SD) AGV from baseline was observed among patients receiving vosoritide up to 15 µg/kg daily. The mean variations in AGV reported from baseline were as follows:

- Cohort 1 at the 2.5 µg/kg dose: -0.371 cm/year (95% CI: [-1.84; 1.10], p = 0.5600);
- Cohort 2 at the 7.5 µg/kg dose: 1.276 cm/year (95% CI: [0.07; 2.48], p = 0.0405);
- Cohort 3 at the 15 µg/kg dose: 2.014 cm/year (95% CI: [0.58; 3.44], p = 0.0111).

At a daily dose of 30 µg/kg, no clinically relevant difference in variation of AGV from baseline compared to Cohort 3 was observed, suggesting that a plateau had been reached in terms of effect.

During the initial 6-months treatment period, an increase in mean AGV of 6.058 cm/year was reported when administered at a dose of 15 µg/kg. This value corresponded to the growth rates observed in children of the reference population (CDC 2017) and supported the proof of concept that vosoritide increases growth rate at a well-tolerated dose. [27] A dot plot of AGV at baseline and 6 months post treatment is presented in Figure 17.

Figure 17. Dot Plot of AGV at Baseline and 6 months posttreatment by cohort (analysis population: efficacy)

Analysis of data relating to the long-term administration of a dose of 15 µg/kg (Cohort 3) and a dose of 30 µg/kg (Cohort 4) confirmed the maintenance of the clinically significant effect observed in terms of AGV over time. Changes from baseline for mean AGV for Cohorts 3 and 4 demonstrate a sustained and consistent treatment effect and are graphically presented in Figure 18.

Figure 18. Changes from baseline for mean AGV for Cohorts 3 and 4, study 111-202

Height Z-score

In line with observed data for AGV, a dose-dependent response was seen for the change from baseline in height Z-scores over the 2-year duration of the study, with an overall 0.8 SDS scores increase in height, suggesting an increase in linear growth compared to the matched general population.

Further improvements in change from baseline in height Z-score were observed over the long-term treatment period. The improvements were consistent and similar between 15 µg/kg and 30 µg/kg dose Cohorts and showed a clinically meaningful difference in height Z-score after 24 months of treatment compared to study baseline. Subjects treated with BMN 111 at 15 µg/kg and 30 µg/kg daily for 6 months had a trend towards improvement in change from baseline in standing height Z-scores compared with average height children, with mean of 0.229 (0.1505) and 0.265 (0.189), respectively [27]. The mean height Z-scores prior to treatment and in the entire study period are presented in Figure 19.

Figure 19. Mean Height Z Scores using CDC reference standard prior to treatment (111-901) and in entire study period - Cohort 3 and 4 (analysis population: efficacy)

Upper to lower body segment ratio

There were no changes in body proportion ratio in any of the cohorts during the initial 6-month treatment period. The mean changes from baseline in upper to lower body ratio in subjects administered daily for 6 months were: 2.5 µg/kg, -0.021 (0.0626), (95% C1 -0.08, 0.04; P=0.4156); 7.5 µg/kg, 0.003 (0.0510), (95% CI -0.04, 0.05; P=0.8719); 15 µg/kg, -0.024 (0.0369), (95% CI -0.05, 0.00; P=0.0743); and 30 µg/kg, -0.030 (0.0811), (95% CI - 0.10, 0.04; P=0.3265). Further, there were no meaningful differences in body proportions over the 24-month treatment period with either dose. As there was no evidence of worsening in body proportion ratios this implies proportional growth effect of vosoritide across upper and lower body segments and upper and lower limb segments. X-ray of the left hand to evaluate potential anatomic abnormalities and to evaluate the progression of skeletal development revealed no abnormal acceleration of skeletal maturity [27].

Safety and tolerability

Administration of vosoritide has been generally well-tolerated in daily doses ranging from 2.5 µg/kg to 30 µg/kg with no change in safety profile over time. All 35 subjects (100%) have experienced at least 1 treatment emergent adverse event during the study. The majority of Adverse Events (AEs) were mild. There have been no deaths or serious adverse events (SAEs) attributed to vosoritide administration [31].

An overview of adverse events over the entire study period is presented in Appendix E.

7.2.2.2 Study 111-205

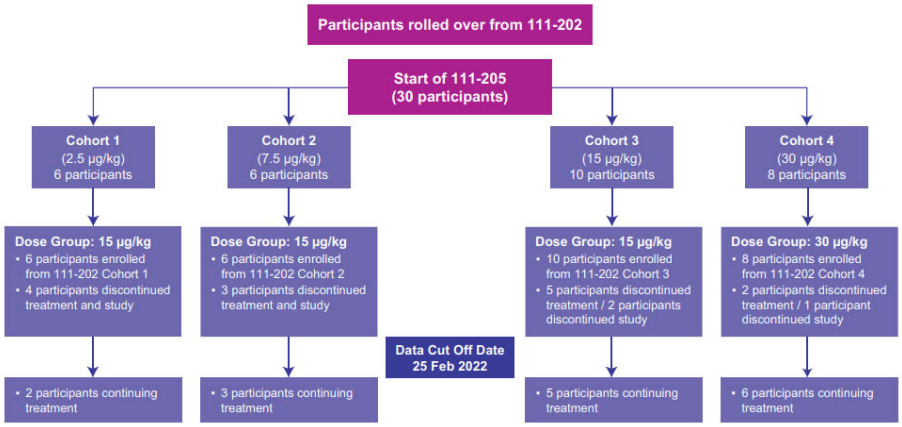
111-205 is an ongoing Phase II open-label, extension study to evaluate the long-term safety, tolerability and efficacy of vosoritide among patients with ACH aged ≥7 years who completed 24 months of vosoritide treatment in Study 111-202.[115] At least 6 months of baseline growth data for all subjects who entered 111-202 was collected in Study 111-901.

Eligible subjects from 111-901 who then completed 2 years of vosoritide treatment in 111-202 were enrolled in the 111-205 extension study to continue receiving the same stable dose of vosoritide received upon completion of 111-202 (15 or 30 µg/kg daily).

As of 25 February 2022, of the 30 participants who entered 111-205, 16 participants were continuing treatment and 20 participants were continuing in the study.

Patient disposition, by cohort, for patients enrolled in study 111-205 is presented in Figure 20. Thirty of the 35 patients from 111-202 were enrolled in 111-205; six patients into each of Cohorts 1 and 2, ten patients into Cohort 3, and eight patients into Cohort 4. After 6 months of dosing in 111-202, patients in Cohorts 1 and 2 titrated to receive 15 µg/kg, while patients in Cohort 3 and 4 continued to receive 15 µg/kg and 30 µg/kg, respectively. As such, all subjects in 111-205 received either 15 µg/kg or 30 µg/kg [115].

Figure 20. Patient disposition for 111-202/205



Five of those who discontinued reached final adult height (FAH)
Source: Hoover-Fong et al, poster presented at ACMG Annual Clinical Genetics Meeting 2023 [116]

Detailed study characteristics is found in Appendix B and baseline characteristics for included patients are the same as those for 111-202 and are presented in Appendix C. Detailed study results are presented in Appendix D.

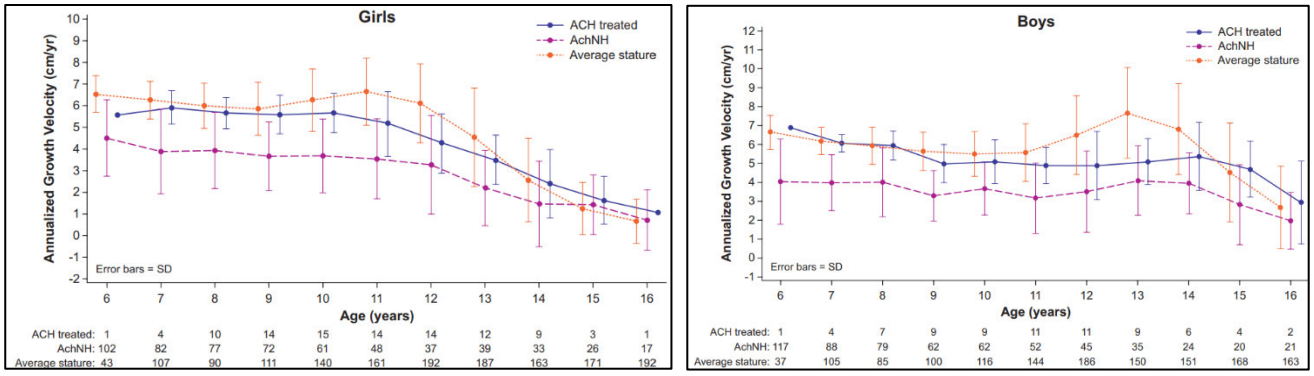
7.2.2.2.1 Key clinical findings

Annualized growth Velocity

The observed improvements in AGV from baseline to Month 6 in 111-202 were sustained throughout the duration of treatment in 111-205. Improvements in cumulative AGV compared to baseline were observed across the four cohorts throughout the duration of treatment. Overall, in participants in Cohorts 1, 2, 3, and 4, the mean (SD) improvement in AGV at Month 72 (N=18) was 1.16 (1.34) cm/year and at Month 78 (N=12) was 0.98 (1.45) cm/year. In participants in Cohorts 1, 2, and 3 (no Cohort 4 participants completed visits from Month 84), the mean (SD) improvement in AGV at Month 84 (N=9, overall) was 1.06 (1.73) cm/year. The results demonstrated improvements in AGV from baseline in all cohorts, which was maintained for up to 7 years [116, 117].

The 12-month interval AGV demonstrated improvement up to Month 60, with a mean (SD) change from baseline in the 12-month interval AGV at Month 60 (N=25) of +0.46 (1.44) cm/year. At Month 72 (N=17), a slight decline was noted with a mean (SD) change from baseline of -0.04 (2.38) cm/year primarily due to the decline in AGV observed in Cohort 1 at -2.49 (2.48) cm/year (Cohorts 2, 3 and 4 show a slight improvement in AGV at 0.15 [1.62], 0.35 [3.31], 0.28 [1.45] cm/year). In participants in Cohorts 1, 2, and 3, AGV at Month 84 (N=8) showed a slight improvement from baseline at +0.13 (3.25) cm/year (decline in AGV in Cohorts 1 and 3 at -2.00 [NA] and -0.77 [3.27] cm/year and an improvement in Cohort 2 at 3.47 [0.33] cm/year) (Figure 21) [116, 117].

Figure 21. Mean 12-month interval AGV in vosoritide treated children is higher compared to age-matched untreated children



AchNH (Ach Natural History) reference derived from CLARITY (Hoover-Fong J et al. Orphanet J Rare Dis. 2021) [113]. Average stature reference is non-African American data from Kelly A et al. J Clin Endocrinol Metab. 2014 [114]
Source: Poster presented at the 2023 ACMG Annual Clinical Genetics Meeting, March 14-18 2023 - Hoover-Fong et al., 2023 [116]

Height Z-score

In line with observed data for AGV, improvement in height Z-score was observed in all Cohorts and were sustained over time. For all Cohorts combined, the overall mean (SD) improvement in height Z-score from baseline at Month 48 and Month 60 was [redacted], respectively; the overall mean change was statistically significant for both timepoints [redacted]. At Month 72, in participants in Cohorts 1, 2, 3, and 4, the mean (SD) improvement in height Z-score was [redacted] standard deviation score (SDS) and at Month 78 (N=12) was [redacted] SDS. In participants in Cohorts 1, 2, and 3, the mean (SD) improvement in height Z-score at Month 84 (N=9, overall) was [redacted] SDS and at Month 90 (N=4, overall) was [redacted] (

Figure 22) [117].

Figure 22. Mean (SD) Height Z-Score Over Time by Cohort: Full Analysis Set

[redacted]

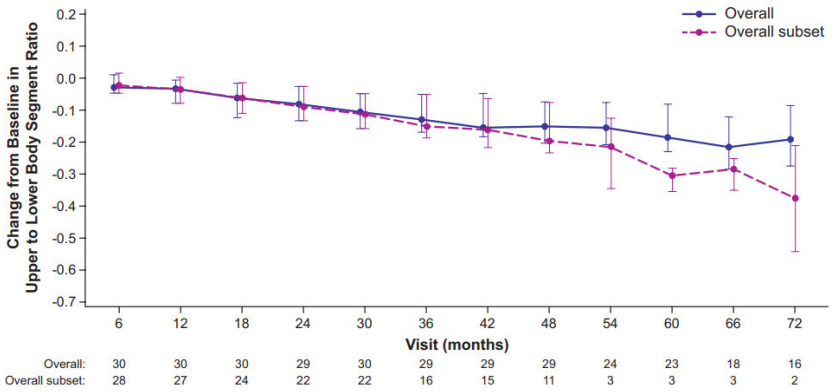
Upper to Lower Body Segment Ratio

Upper to lower body segment ratios continued to improve over time, with changes particularly marked in the subset of children aged < 11 years (girls) / < 12 years (boys) in whom there may be more opportunity to impact this parameter (Figure 23) [116].

Overall, in participants in Cohorts 1, 2, 3, and 4, the mean (SD) improvements in upper to lower body segment ratio at Month 72 (N=16) was [redacted] and at Month 78 (N=12) was [redacted]. In participants in Cohorts 1, 2, and 3, the mean (SD) improvements in upper to lower body segment ratio at Month 84 (N=9, overall) was [redacted] and at Month 90 (N=4, overall) was [redacted] [117].

For all Cohorts combined, the overall mean (SD) change in upper to lower body segment ratio from baseline at Month 48 and Month 60 was [redacted] and [redacted] respectively; the overall mean change was statistically significant for both timepoints [redacted]

Figure 23. Upper to lower body segment ratios over time



Overall subset: Proportionality changes up to ~age 11 (girls) / 12 (boys). Older children excluded from analysis given any treatment is unlikely to impact proportionality beyond this point.
Source: : Poster presented at the 2023 ACMG Annual Clinical Genetics Meeting, March 14-18 2023 - Hoover-Fong et al., 2023 [116]

Safety and tolerability

Long term treatment with vosoritide at daily doses of 15 or 30 µg/kg was well tolerated. All 30 (100%) subjects reported at least 1 AE and 29 (96.7%) subjects reported any treatment-related AE during the 111-202/205 studies, with a similar incidence reported between all four Cohorts. The majority of AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2, with 8 (26.7%) subjects reporting Grade 3 (severe) AEs, all considered not related to study treatment with no unexpected safety findings, except for 1 event of kyphosis in cohort 4, which was non-serious, did not lead to any study drug dose modification. In addition, one serious Grade 4 event of circulatory collapse (verbatim: collapse after removal of vascath line requiring resuscitation) was reported in Cohort 4 > 30 days after the last dose of study drug. Injection site reactions were the most commonly reported AEs and were all non-serious and transient. No SAE was considered to be related to study drug, and no deaths occurred. One subject withdrew from the study in 111-205 due to a non-serious AE of transaminases increased. There were no AEs leading to dose reduction. [93, 115]

An overview of adverse events over the entire study period is presented in Appendix E.

7.2.2.3 Conclusions 111-202 and extension study 111-205

The efficacy results of 111-202 and its extension study 111-205 demonstrated improvements in AGV in all cohorts, which were maintained for up to 7.5 years, taking into consideration natural decline in AGV observed in untreated children with ACH in this age range [35, 118]. Increase in AGV resulted in improvements in height Z-score relative to average stature children and a continuous improvement in height Z-score referenced to ACH untreated participants. A total of five participants reached NFAH. There was no worsening of body proportion and a trend for upper to lower body segment ratio to improve over time [116, 117].

7.2.2.4 Study 111-206

111-206 was a Phase II, multicenter, randomized, double-blind, placebo-controlled trial in infants and younger children with ACH conducted in 16 study centers across four countries (US, Australia, UK, Japan) [29]. The primary objective was to evaluate the safety and tolerability of vosoritide in children aged 0 to <60 months, for up to 52 weeks of treatment with 2 weeks safety follow up. Key secondary objectives included to evaluate the effect of vosoritide on growth parameters and on QoL, developmental status, and functional independence [119].

Subjects were enrolled into three age Cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects are stratified by age:

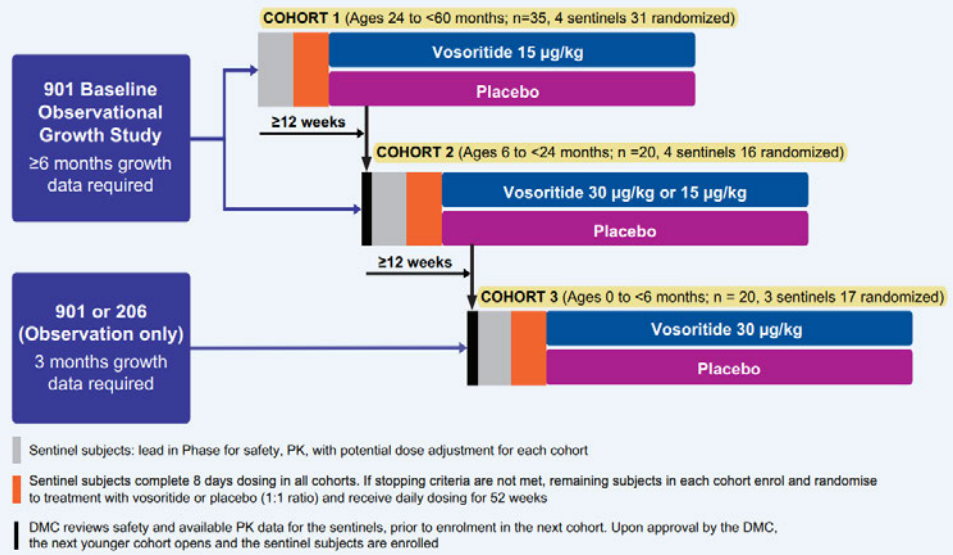
- **Cohort 1** - children aged ≥ 24 to < 60 months (stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- **Cohort 2** - children aged ≥ 6 to < 24 months (stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- **Cohort 3** - children aged 0 to < 6 months. Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

It should be noted that treatment of patients within cohort 2 and 3 are outside the currently licensed indication and thus outside the scope of this submission why results from these cohorts are not presented.

Patient disposition for patients in study 111-206 is presented in Figure 24. A total of 75 participants (full analysis set [FAS]) were enrolled into the study, of which 64 participants were randomized to receive vosoritide or placebo, which constituted the FAS (randomized) and was considered the primary analysis population for the efficacy assessment, and 11 participants were enrolled to receive vosoritide (sentinel participants) [119]. A total of 35 patients were enrolled to cohort 1.

Detailed study characteristics is found in Appendix B and baseline characteristics of patients is found in Appendix C. Detailed study results are presented in Appendix D.

Figure 24. Study design and patient disposition of 111-206



Note: Treatment of patients within cohort 2 and 3 are outside the currently licensed indication and thus outside the scope of this submission

Source: Poster presented at the Endocrine Society's 2022 Annual Meeting, June 11-14, 2022, Atlanta, GA, Savarirayan 2022 [94]

7.2.2.4.1 Key clinical findings

Detailed study results are presented in Appendix D.

Efficacy analyses were performed on the overall population FAS (randomized) and FAS, and by cohorts. ANCOVA models were used to estimate the treatment effect including baseline covariates, which adjusted for imbalances and reduced the overall variability. Results from the licensed indication, cohort 1, are reported here.

Height Z-score

As expected, and driven by natural age-related changes in linear growth, baseline growth patterns differ substantially between the cohorts. Cohort 1 (age group ≥24 to <60 months), shows relatively stable and predictable baseline growth.

In Cohort 1, the LS mean difference for change from baseline in height Z-score was [redacted] compared with placebo in the FAS (randomized) population (Figure 19). Similar results were observed in the FAS population (LSM difference of [redacted] in Cohort 1 [119] (Table 11). These results are consistent with z-score improvements in >5year old patients.

In Cohort 1, with less variable baseline growth, an improvement in height Z-score was observed in vosoritide participants compared with placebo (LSM difference of [redacted] [119]. The LS mean change from baseline for height Z-score for the different cohorts are graphically presented in Figure 25 [94].

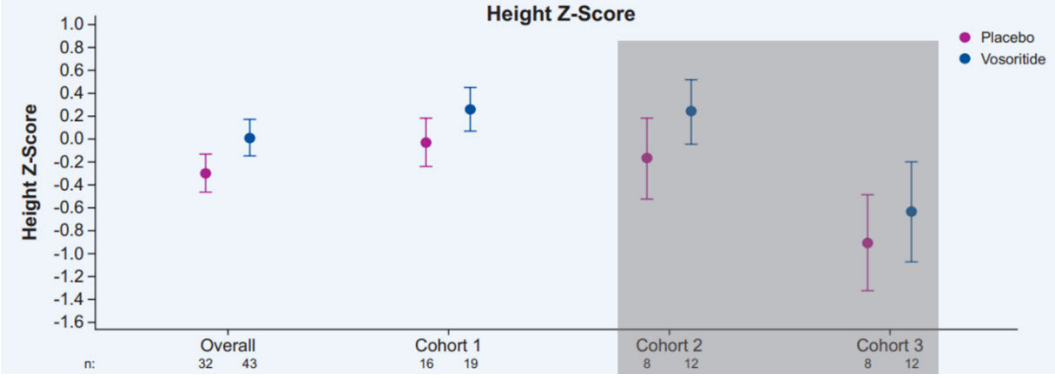
Table 11. Analysis of Covariance of Height Z-score at Week 52

Full Analysis Set (randomized)								
Height Z-Score	**Cohort 1**		Cohort 2		Cohort 3		**Overall**	
	Placebo	Vosoritide	Placebo	Vosoritide	Placebo	Vosoritide	Placebo	Vosoritide
N	[redacted]							
Baseline, mean (SD)	[redacted]							
LSM change From Baseline (95% CI)	[redacted]							
Difference in LSM (95% CI)[a]	[redacted]							

Full Analysis Set (randomized)												
p-valueb	[redacted]		[redacted]		[redacted]		[redacted]					
	Full Analysis Set											
N	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
Baseline, mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
LSM change From Baseline (95% CI)	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
Difference in LSM (95% CI) [a]	[redacted]				[redacted]				[redacted]			
p-value[b]	[redacted]				[redacted]				[redacted]			

Note: (grey italic font) Treatment of patients within cohort 2 and 3 are outside the currently licensed indication and thus outside the scope of this submission.
CI: confidence interval; FAS: full analysis set; SD: standard deviation
a Difference is vosoritide minus placebo.
b Two-sided p-value.
c Based on 10 imputed datasets. LS means and difference in LS means were obtained from an analysis of covariance model. Model terms included treatment, sex, age stratum, baseline age, baseline AGV and baseline height Z-score.
Source: BioMarin Final Clinical Study Report 111-206, 2022 [119]

Figure 25. Height Z-score at Week 52 (Analysis Population FAS [randomized])



Note: (grey overlay) Treatment of patients within cohort 2 and 3 are outside the currently licensed indication and thus outside the scope of this submission.
Source: Poster presented at the Endocrine Society's 2022 Annual Meeting, June 11-14, 2022, Atlanta, GA, Savarirayan 2022 [94].

Standing height

At week 52, a greater increase in height was observed in the vosoritide group compared with placebo in all cohorts. The improvement in height was aligned with the positive impact of treatment on height Z-score in Cohort 1 with LS mean difference of [redacted] in favour of vosoritide compared to placebo [119]. Similar results were observed in Cohort 1 in the FAS population [redacted] [119]. ANCOVA analysis of height at Week 52 in vosoritide compared with placebo for all cohorts is illustrated in

Figure 26. The overall baseline heights were consistent with the age range of the individual cohorts [119].

Figure 26. LS Mean Change from Baseline (95% CI) for Standing Height at week 52. Analysis Population (Full Analysis Set [Randomized])

Annualized growth velocity

At week 52, treatment with vosoritide demonstrated a positive impact of therapy through a marked increase in AGV of approximately [redacted] compared to placebo in the overall population (FAS [randomized]) [119].

The LS mean difference between the treatment groups was consistent across the cohorts with point estimates in favor of vosoritide. Cohort 1 placebo showed an increase in AGV at Week 52, with a marked increase seen in the vosoritide group (LSM difference of [redacted] Similar results were observed in the FAS population (LSM difference of [redacted] [119]. The ANCOVA analysis of AGV at Week 52 in vosoritide compared with placebo is illustrated in Figure 27.

Figure 27. LS Mean Change from Baseline (95% CI) for Annualized Growth. Analysis population (Full Analysis Set [Randomized])

Upper to Lower Body Segment Ratio

There were no clinically significant changes in body proportions at Weeks 26 and 52. [119].

Health-related quality of life

Results interpretation for HRQoL, functional independence, and developmental performance, as measured by ITQoL, WeeFIM®-II, and (Bayley Scales Of Infant and Toddler Development) BSID-III, is limited due to small sample sizes, and heterogeneity introduced by developmental stage and age preclude the ability to draw meaningful inferences within a 52-week timeframe [119].

Safety and tolerability

An overview of AEs occurring in the Safety Population from baseline to the most recent data cut (September 2019) is presented in Appendix E.

The duration of treatment during the study was comparable between the all-vosoritide and placebo group (mean [SD]: 363.0 [25.3] days and 365.5 [10.2] days, respectively).

Vosoritide was well tolerated, with no treatment limiting adverse effects and a safety profile generally consistent with that seen in older children in the phase 3 pivotal study (111-301). No new safety concerns were identified with use of vosoritide in participants aged 0 to <5 years. A total of 37 (86.0%) all-vosoritide participants and 17 (53.1%) participants in the placebo group reported at least one treatment-related AE. Most AEs were mild (Grade 1) or moderate (Grade 2) and, other than injection site reactions (ISRs), were typically associated with childhood illness or ACH related events. No clinically relevant difference in the nature and pattern of AEs, SAEs, or laboratory assessments were observed across cohorts. Two (4.7%) participants in all vosoritide group and 3 (9.4%) placebo participants reported at least one Grade ≥3 AE; none of the Grade ≥3 AEs were assessed as related to the study treatment and all were reported in Cohort 3 only. Nine participants (3 all-vosoritide and 6 placebo participants) reported 11 treatment-emergent SAEs; no SAEs were assessed as related to study treatment. Most SAEs were due to childhood related illnesses or to developmental milestones in children. SAEs were more frequent in Placebo group (18%) compared to Vosoritide-treated group (7%). All SAEs including fatal event in treatment group were unrelated to treatment. There was no evidence of disproportionate skeletal growth, accelerated bone age, or abnormal bone morphology; there were no trends related to AEs in the neurological or psychiatric disorders SOC; there was no evidence of any off-target CNS effects, and there were no abnormal hip examinations reported for any participant during the study. There was no evidence of changes in behavior, in particular anxiety or depression, during the study. There was one case of death, sudden infant death syndrome, in a 1-year-old child on Vosoritide participating in the 111-206 study. There were significant pre-existing health conditions and the death was assessed to be not related to the study drug by safety teams, the Principal Investigator, and the Data Monitoring Committee [119] [94].

7.2.2.4.2 Conclusion

Phase II study 111-206 shows positive growth trends in sentinel patients treated with vosoritide in children with ACH aged 0 to < 5 years. The magnitude of height deficit between sentinel subjects and average stature children, measured by the height Z-score, decreased following treatment with vosoritide. A positive improvement in growth was also observed on the basis of other anthropometric measures, particularly in terms of AGV and standing height, with a mean variation (SD) in standing height compared to baseline in Cohort 1 [redacted] cm at 52 weeks.

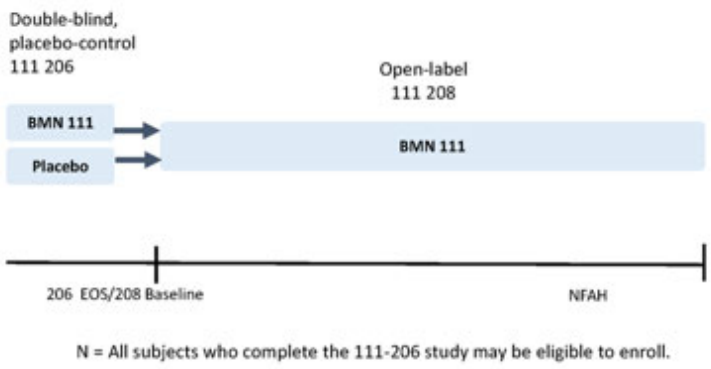
Following completion of the study, subjects in all treatment groups are eligible to receive vosoritide in an open-label extension study, to assess safety and efficacy of longer- term treatment with vosoritide (111-208) [94].

7.2.2.5 Study 111-208

111-208 is an ongoing Phase II open-label, multicenter long-term extension trial to evaluate the safety and efficacy of vosoritide in children with ACH who complete 1 year of vosoritide or placebo treatment in the parent trial 111-206. Primary endpoints are long-term safety and compatibility, and height z-score. Key secondary objectives include to evaluate the effect of vosoritide on AGV, body proportions and QoL. Patients who enroll will continue to be evaluated until they reach near FAH (defined as evidence of growth plate closure and <1.5 cm/year AGV).[29]

At the January 26, 2022, data cut point, 73 patients from 111-206 trial were enrolled and receiving vosoritide. At baseline, 11 patients were 0 to <6 months of age, 22 patients were ≥6 to <24 months of age, 34 patients were ≥24 to <60 months of age, and 6 patients were ≥60 months of age. In total, 42 patients had already received vosoritide in the BMN 111-206 trial, and 31 switched from placebo in BMN 111-206 to vosoritide in BMN 111-208 [32].

Figure 28. Study design of the 111-206 and 111-208 study



Source: BioMarin 2023, 111-208 interim clinical study report [32].

Baseline was defined as the last assessment before the first dose of vosoritide. Therefore, for participants who were already receiving vosoritide in the BMN 111-206 study (vosoritide/vosoritide group), the baseline assessment was the same as in the 111-206 study. For participants who did not receive vosoritide until the BMN 111-208 extension study (placebo/vosoritide group), baseline data were obtained immediately before the first dose was administered in 111-208 [32].

Detailed study characteristics is found in Appendix B and baseline characteristics of patients is found in Appendix C. Detailed study results are presented in Appendix D.

7.2.2.6 Key clinical findings

For the indication to be evaluated (achondroplasia ≥2 years), only the age group ≥24 to <60 month and age group ≥60 months are relevant.

Annualized growth velocity

In subjects aged ≥24 months, following the natural pattern of growth velocity deceleration in this age group, a positive change in mean AGV from baseline was observed in all but two time points. In subjects aged ≥24 to <60 months, the mean (SD) AGV [redacted]. The mean (SD) change from baseline was positive at all time points except two [redacted] In subjects aged ≥60 months, mean AGV was >5 cm per year at each measurement time point after baseline [32].

Height z-score

Among participants aged ≥ 24 to < 60 months, mean height z-score (SD) improved from [redacted] at week 52 (N = 33). The corresponding mean (SD) change from baseline was [redacted] A total of 21 participants were followed up to week 104. For these participants, the mean (SD) height z-score improved to [redacted] at week 104. The corresponding mean (SD) change from baseline at week 104 [redacted] A similar trend of numerical improvement in mean (SD) height z-score was observed in participants aged ≥ 60 months, improving from [redacted] he last visit for which data were available from 5 participants, with corresponding changes from baseline of [redacted] at weeks 52 and 78 [32].

Figure 29. Mean (+/- SD) change in z-score - FAS line plots of height z-score across time by baseline age group

Upper to lower body segment ratio

In all age groups, there was a decline in the upper to lower body segment ratio over time which is consistent with the natural pattern of growth in this age group of participants with ACH. Due to the natural improvement (decline) in upper to lower body segment ratio, and in absence of the untreated control group, it is not clear whether treatment with vosoritide was associated with clinically meaningful incremental improvement in proportionality.

Figure 30. Upper to Lower Body Segment Ratio Over Time by Baseline Age Group (Mean +/-SD) – All Treated (FAS)

Safety

Almost all patients in the age groups ≥24 to <60 months and ≥60 months experienced any adverse event of the adverse events in the ≥24 to <60 months age group and none of the adverse events in the ≥60 months age group were attributable to medication. serious adverse events occurred in the ≥24 to <60 months age group in the ≥60 months age group None of the serious adverse events were

considered causally related to treatment. [redacted] event in the age group ≥24 to <60 months had a CTCAE severity ≥ [redacted] In the age group ≥60 months, there were [redacted] None of the patients died during the observation [32]. Safety details are presented in Appendix E.

7.2.2.7 **Study 111-209** (ongoing, no results)

This is a 2-year open label randomized controlled trial of vosoritide in infants with ACH ages 0 to 12 months.[95] Approximately 20 infants will be randomized 1:1 to either open label once daily subcutaneous vosoritide combined with standard of care or standard of care alone. The primary and secondary aims of the study are to evaluate the safety and efficacy of vosoritide in children with cervicomedullary compression at risk of requiring decompression surgery. The trial will be carried out in specialized skeletal dysplasia treatment centers with well-established multidisciplinary care pathways and standardized approaches to the neurosurgical management of cervicomedually compression. After 2 years, infants randomized to standard of care alone will be eligible to switch to vosoritide plus standard of care for an additional 3 years. This pioneering trial hopes to address the important question as to whether treatment with vosoritide at an early age in infants at risk of requiring cervicomedullary decompression surgery is safe and can improve growth at the foramen magnum and spinal canal alleviating stenosis. This study is under recruitment and no results are available at this time. [95]

Safety

Long-term administration of vosoritide was generally well tolerated. In the occurrence of adverse events due to vosoritide administration, the age group ≥24 to <60 months and the age group ≥60 months showed no major differences. There were no deaths and no serious events associated with study medication.

Almost all 40 (97.5%) subjects reported at least one AE during the 111-208 study. Only for one patient in the younger age group no adverse event was reported. [redacted] SAEs were reported in the age groups considered, three of which occurred within the younger age group and two of which occurred in the older age group. All SAEs were assessed as unrelated to vosoritide treatment. There were no deaths. None of the cases resulted in treatment or study discontinuation. There were [redacted] that resulted in dose interruption. [redacted] subjects reported at least one grade 1 AE, [redacted] subjects reported grade 2, and [redacted] subjects reported grade 3. EOIs occurred only in the age group ≥24 to <60 months. The most common event was hypersensitivity with [redacted] in this age group [redacted] This is followed by injection site reactions with an incidence of [redacted]

The most frequently reported AEs in the two cohorts considered were infections and infestations, followed by respiratory, thoracic, and mediastinal diseases, gastrointestinal diseases and injuries, poisonings, and procedure-related complications. Clinically significant differences in incidence and event rates for specific AEs were observed between age groups, but this may be attributable to low numbers in the ≥60-month age group.

7.2.3 Natural history studies

Three non-interventional, observational natural history studies, 111-901, 111-501 and 111-502, have investigated the natural history of patients with ACH.

7.2.3.1 Study 111-901

111-901 was a prospective, multicenter, multinational study that collects specific growth measurements of pediatric patients with ACH [98]. Patients enrolled in 111-901 were assessed for their suitability for enrolment in subsequent BioMarin sponsored clinical trials. A total of 363 children were enrolled (28 centers, 8 countries). The enrolled patients underwent growth measurements at baseline and then subsequently at three-monthly intervals until completion of the study. Subjects with previous limb-lengthening surgery may have been enrolled if surgery occurred at least 18 months prior to the study and healing was complete without sequelae [98].

Primary objective was to collect baseline growth measurements on pediatric patients with ACH, including: Annual Growth Velocity (AGV), Height Z-Score, Standing or sitting height, Upper to lower body segment ratio and Other body proportion and growth measures. Secondary objectives included health related quality of life, functional independence and ADL questionnaires, AEs, clinical laboratory tests, and vital signs.

The baseline characteristics reflect the epidemiology of ACH and the geographic distribution of recruiting countries. Overall, at the 111-901 baseline, the 363 subjects included in this study were aged from newborn to 13.5 years, with a mean (SD) and median age of 5.14 (3.32) and 5.09 years. Mean (median, range) age at the 111-901 baseline by subsequent study enrollment reflected the entry criteria of those studies:

- 6.62 (6.32, 4.5 to 9.7) years for 111-202 enrolling subjects (n=35);
- 6.97 (6.48, 2.8 to 13.4) years for 111-301 enrolling subjects (n=121); and
- 1.31 (0.98, 0.0 to 4.0) years for 111-206 enrolling subjects (n=69).

Across all groups by subsequent enrollment, including those not enrolled into a drug study, there was a balance of male and female subjects and most were Caucasian (74.9% overall) [98].

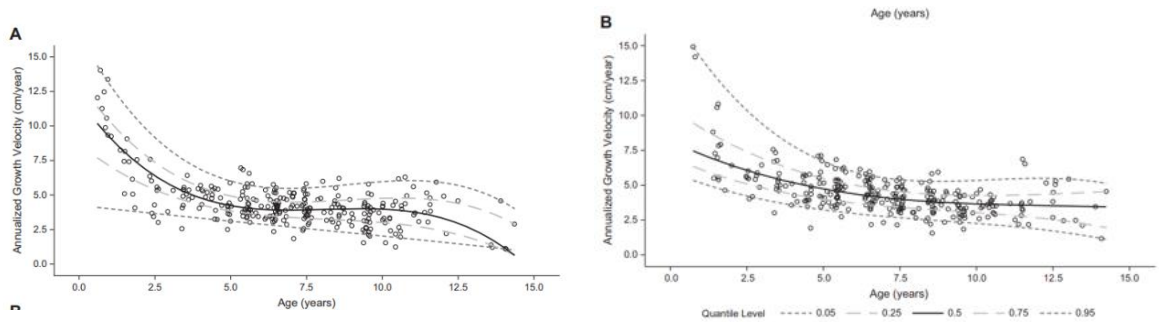
Detailed study characteristics is found in Appendix B and baseline patient characteristics of patients in studies used for the comparative analysis of efficacy and safety for vosoritide are found in Appendix C. Detailed study results are presented in Appendix D.

7.2.3.1.1 Key clinical findings

Annualized growth velocity

The age specific AGV of the subjects in Study 111-901 was similar to that of the published data with a maximum deficit in height accumulated between the ages of 0 and 2 years. Thereafter, as reported in the literature, a small decrease in AGV was observed throughout the first decade (Figure 31 A & B). Among participants aged <1 year, mean AGV was 11.6 (1.7) cm/year for girls and 14.6 (0.5) cm/year for boys. By age 1 year, mean AGV decreased to 7.1 (1.7) cm/year in girls and 7.4 (2.1) cm/year in boys. By age 10 years, mean AGV was approximately 3.6 (1.3) cm/year for girls and 3.6 (0.6) cm/year for boys. The number of participants aged >12 years was small and consequently the variability associated to the integer point estimates for the growth parameters increased for the later years [98].

Figure 31. Scatter plots with cubic quantile regression curves of annualized growth velocity (AGV) from birth to 15 years in (A) female children and (B) male children.



Black circles represent AGV for an individual participant where age is the midpoint for the AGV interval of 12 months ± 3 months. The dashed lines represent cubic quantile regressions for the 95th, 75th, 50th, 25th, and 5th quantiles. For each participant one AGV associated to each integer year is retained for the plot. Plots based on full analysis set excluding AGV based on height assessments following limb lengthening, growth hormone, or other investigational treatments and erroneous AGV assessments <0. Source: Savarirayan 2022 [98].

Height Z-score

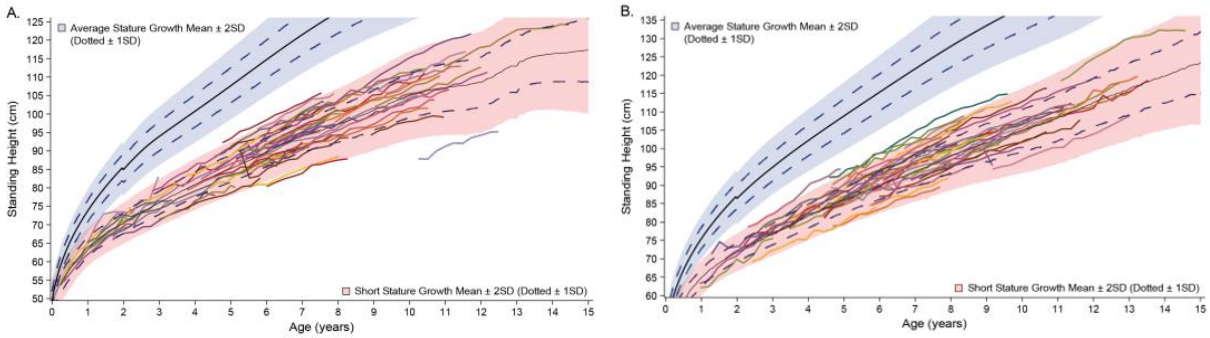
For subjects from 0 to 24 months for whom body length was available, the Z-scores were derived using WHO references and macro [120]. Data are presented as SDS above or below the age-specific reference (which is equivalent to 0). Short stature is defined as a height of ≥ 2.0 SDS below the population-specific mean height for age and gender[121]. Mean height z-score in those aged <1 year was −2.5 (1.0) SDS for girls and −3.2 (1.2) SDS for boys, compared with average stature children of a similar age and sex. Mean height deficit increased up to the age 5 years (mean z-scores of −5.3 [1.1] SDS for girls and −4.6 [0.8] SDS for boys). Compared with average stature children of a similar age, the mean height

deficit of patients with ACH, as measured by Z-scores, was substantial throughout childhood for both females and males. The height deficit increased in patients up to 5 years of age and, despite increasing variability after 5 years of age, remained high in all age groups throughout the study [98]..

Standing height

The standing height values of ACH patients were lower than those of average stature age- and sex- specific reference data across all ages and are consistent with published data on ACH, [98].

Figure 32. Standing heights for (A) girls and (B) boys over time according to age (full analysis set with ≥2 years of follow-up)



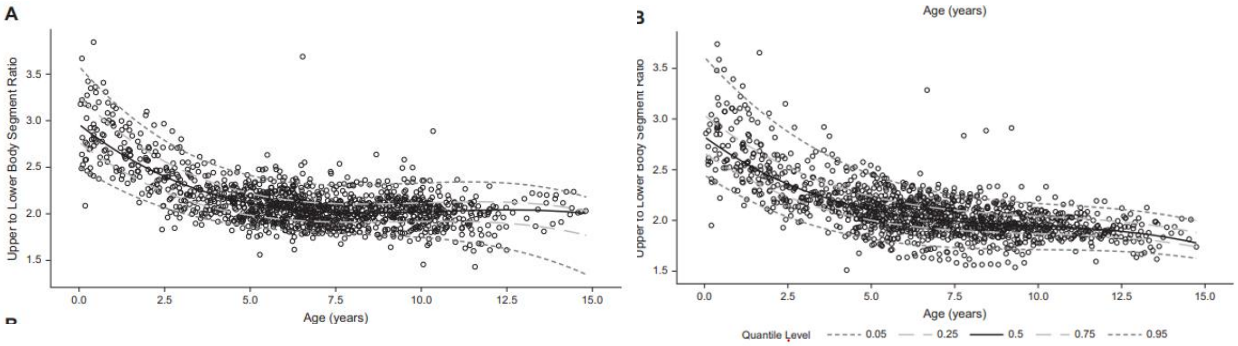
SD; standard deviation. Colored lines represent standing height measurements by age for individual study participants. Reference ranges for average stature children are shown in the blue shaded area and were derived using age-sex specific reference data (means and SDs) per the Centers for Disease Control and Prevention. Reference ranges for achondroplasia are derived from Hoover-Fong et al., 2017 [34]. Sources: Savarirayan, 2022 [98].

Upper to lower body segment ratio

Average stature children aged <2 years have an upper to lower body segment ratio of ~1.4,[35] which decreases to about 1.1 by the age of 5-6 years and reaches a final value of 1 by the age of 10 years. In contrast, disproportionate growth in the lower limbs of ACH patients causes the upper body to represent a greater proportion of total height than the lower body and published data show that the mean value at birth is about 2.6, rising to about 2 at age 5-6 and peaking at about 1.8 at age 10 [35, 122].

In this study, both girls and boys had a disproportionate upper-to-lower body segment ratio (). Mean ratio was highest for girls and boys aged <1 year (girls 2.9 [0.6]; boys 2.8 [0.4]) and decreased gradually to approximately 2 for both sexes from age 4 years [98].

Figure 33. Scatter plots and cubic quantile regression curves of upper-to-lower body segment ratio from birth to 15 years in (A) female children and (B) male children



Black circles represent AGV for an individual participant where age is the midpoint for the AGV interval of 12 months ± 3 months. The dashed lines represent cubic quantile regressions for the 95th, 75th, 50th, 25th, and 5th quantiles. For each participant one AGV associated to each integer year is retained for the plot. Plots based on full analysis set excluding AGV based on height assessments

following limb lengthening, growth hormone, or other investigational treatments and erroneous AGV assessments <0. Source: Savarirayan, 2022 [98].

Quality of Life and Activities of Daily Living

PedsQL: Standard PedsQL reference values for child quality of life are based on a large healthy pediatric sample (N = 9566) aged between 2 and 18 years for self- and parent/carer-reports [75]. Compared to this healthy reference population, self- and carer-reported PedsQL scores for ACH patients were reduced across physical, social and school functioning domains [25, 75]. Summary scores, which combine the scores from relevant domains (physical summary score: physical functioning domain; psychosocial summary score: social, emotional and school functioning domains; total summary score: all domains), for ACH patients included in the study were also lower than the average stature population values [75]. The exception was the emotional functioning domain (which includes expressions like feelings of anxiety, sadness, anger, worry, and sleep difficulties), where values in children with ACH appeared similar to the healthy reference population [25].

The mean (SD) total score reported by parents/caregivers was [redacted] for patients <1 year of age, with a trend of decreasing mean total scores with age. The mean total score (SD) reported by parents/caregivers for children 12 years of age and older was [redacted] The mean total score (SD) reported by parents/caregivers was 82.70 (15.40) in the reference population [75].

The mean total score reported by the children showed a trend of increasing with age. The total score reported by children from age 8 years was [redacted] and from age 12 years was [redacted] The mean total score (TS) was 83.84 (12.65) in the reference population [75].

QoLISSY*:* The QoLISSY tool was used as a patient-reported questionnaire for patients aged ≥ 12 years, reported by parents of children aged 4 to 18 years. Overall, data from the QoLISSY questionnaire showed that for physical, social, and emotional domains, values were similar between all ages. Of all five patient-rated domains (physical, social, emotional, coping, and belief), coping scored the lowest.[25] However, coping and belief scores tended to increase for patients aged 10 years and above, suggesting that as a child gets older, the parent and child cope better with the condition and general beliefs improve.[25] Comparisons between QoLISSY data from patients included in 111-901 and average stature individuals have not been conducted. No trend was observed in terms of total score reported by parents/caregivers or children, although the mean total score reported by parents/caregivers was generally slightly lower than that reported by children for the respective age groups.

WeeFIM®*:* Carer-/patient-reported WeeFIM data showed that functional performance across the three measured domains (self-care, mobility and cognition) improved with age, suggesting that ACH can develop this functional performance over time. However, milestones were delayed across all ages in self-care and mobility compared with normative data; patients with ACH required greater caregiver assistance for longer for self-care and mobility than typically developing children without ACH.*[123]* The exception was for social cognition which was similar for ACH patients and the healthy reference population [25].

Symptoms and complications

During the study, a high proportion of patients experienced at least one disease-related symptom or complication. Three patients discontinued from the study due to these events; two due to the need for surgery for cervical spinal stenosis and one due to elevated blood alkaline phosphatase (ALP). A summary of the symptoms and comorbidities experienced by patients in 111-901 baseline is presented in Table 12.

Table 12. Symptoms, comorbidities and burden of illness for patients with ACH from 111-901

Symptom/complication , %	111-901 population (N=342)
Patients with any symptom/complication	[redacted]
Symptom/complication leading to study discontinuation	[redacted]

Symptom/complication , %	111-901 population (N=342)
Patients with any symptom/comorbidity of CTCAE grade ≥3	[redacted]
Patients who died	[redacted]
Tonsillectomy	[redacted]
Sleep apnoea	[redacted]
Limb and spine deformities/procedures	
Spinal decompression	[redacted]
Bowing of long bones	[redacted]
Kyphosis	[redacted]
Lordosis	[redacted]
Knee deformity	[redacted]
Limb deformity	[redacted]
Hand deformity	[redacted]
Cervical spinal stenosis	[redacted]
Skull deformities/complications	
Foramen magnum stenosis	[redacted]
Skull malformation	[redacted]
Macrocephaly	[redacted]
Nervous system disorders	
Speech disorder	[redacted]
Hypotonia	[redacted]
Hydrocephalus	[redacted]
Pain	
Pain in extremity	[redacted]
Back pain	[redacted]
Neck pain	[redacted]

Source: BioMarin, Clinical study Report 111-901, 2021 [25]

Safety

All reportable events during the 111-901 study were considered AEs according to the protocol: any untoward medical occurrence (e.g., sign, symptom, illness, disease, or injury) in a subject, regardless of attribution to study procedure(s). Any worsening of ACH-related medical histories was reported as AEs. Overall, [redacted] of subjects experienced at least one AE, [redacted] experienced an AE of Grade 3 or higher severity, and [redacted] experienced at least one SAE [25]. Four subjects discontinued from the study due to an AE or SAE (three due to the need for surgery for cervical spinal stenosis and one due to elevated blood ALP); one subject died during the study [25].

Detailed safety information is found in Appendix E.

7.2.3.2 Study 111-501

Study 111-501, Lifetime impact of achondroplasia study in Europe (LIAISE) was a multinational, observational study of medical care, QoL, HCRU and costs, and socio-economic, clinical, and psychosocial burden in patients with ACH in Europe[9, 97]. Demographic and clinical characteristics, as well as HCRU, were extracted from the patients' medical records as part of a clinical chart review [9]. Demographic and clinical characteristics, as well as HCRU, were extracted from the patients' medical records as part of a clinical chart review. In addition, patient-reported outcomes were recorded via a study questionnaire, administered as part of the patients' routine hospital visits (or sent by post if the patient was not attending a hospital) [9, 97].

In total, 195 subjects were enrolled in the study [97]. The sample size was mainly based on feasibility considerations. The study was opened to enrolment for all individuals with ACH who were ≥ five years of age. Among the 195 subjects enrolled, 186 completed the study (provided medical history data and completed and returned the questionnaires) and were included in the full analysis set (FAS). The FAS included all consented subjects with a documented diagnosis of ACH per the inclusion electronic case repot form (eCRF) page and historical data available (i.e., general medical history, prior medications, medical or surgical examination history, procedural treatment history, surgical history, healthcare resource use) [9, 97]. Among these, 97.3% had at least 5 years of historical data collected.

Detailed study characteristics is found in Appendix B and baseline characteristics of patients is found in Appendix C. Detailed study results are presented in Appendix D.

7.2.3.2.1 Key clinical findings

At least one complication or surgery was reported for 94.6% and 72.0% of patients, respectively, at a rate of 66.6 and 21.5 events per 100 person-years. Diverse medical and surgical complications were reported for all ages in a bimodal distribution, occurring more frequently in the youngest and oldest age groups. A total of 40 patients had previously undergone limb lengthening (capped at 20% per the study protocol). The most frequent surgery types varied by age, in line with complication profiles [97].

Standing height

Data on standing height were available in 173 patients. As is typical in ACH populations, patients included in LIAISE showed an increase in standing height throughout childhood, which then ceased as patients reached adulthood [9, 34]. FAH in LIAISE was ~130–150 cm, which is similar to other published estimates for ACH populations, and substantially lower than is reported in average stature individuals [9, 34, 124].

Quality of Life and Activities of Daily Living

PedsQL*:* The PedsQL questionnaire was completed by 105 children (5–17 years old; 17 with limb lengthening and 88 without) and 97 parents of patients aged 5–17 years (16 patients with limb lengthening and 81 without). Across both patient- and parent-completed questionnaires, the lowest mean (SD) domain scores were observed for Physical Functioning and School Functioning. Across all domains, both patient- and parent-reported scores were lower than those of age-matched average stature individuals indicating that patients with ACH experienced poorer QoL [9]. The mean PedsQL total score (child and parent versions) was lower among the children and adolescents of the modified Full Analysis Set (FAS) population than in the healthy reference population (for the child version: 69.3 [SD: 16.3] vs. 83.8 [SD: 12.7], respectively; for the parent version 67.6 [SD: 16.8] vs. 82.7 [SD: 12.7], respectively) [125].

QoLISSY*:* The QoLISSY questionnaire was completed by 67 children (8–17 years old; 16 with limb lengthening and 51 without) and 108 parents of children aged 5–17 years (17 patients with limb lengthening and 91 without). Parent-reported scores were lower than patient-reported scores across the majority of domains, but in both groups the lowest scores were reported in the Physical and Coping domains. The patient- and parent-reported scores for all respondents were lower than average stature individuals (in this case defined as individuals <2 SDs below average height) across the majority of domains, and particularly in the Physical domain [125]. The mean QoLISSY total score was 58.0 (SD: 21.8) overall (0: poor quality of life; 100: perfect quality of life), and respectively 63.4 (SD: 22.2) for the child questionnaire and 54.8 (SD: 21.0) for the parent questionnaire [97].

WeeFIM®: Functional independence among patients aged 5–17 years old was assessed using the WeeFIM questionnaire, which was completed by a total of 104 patients (16 with limb lengthening and 88 without). The mean (SD) WeeFIM total score was 112.7 (13.3) (possible score range: 18 [total assistance] to 126 [complete independence]). The mean (SD) score for the Mobility domain, which has a score range of 5 (total assistance) to 40 (complete independence) was 31.4 (4.6). The mean (SD) score for the Cognition domain (which had the same score range as the Mobility domain) was 33.6 (2.9). Self-care was the domain for which patients reported the greatest level of independence, with a the mean (SD) score was of 47.7 (8.4) (possible score range: 8 to 56) [97].

Quality of life: A total of 74 adults completed the EQ-5D-5L questionnaire (21 with limb lengthening and 53 without). The domain with the greatest proportion of patients reporting moderate to extreme problems was pain/discomfort (37.9%), followed by mobility (17.7%). The mean (SD) VAS score was 73.9 (18.9), and the mean (SD) index score was 0.7 (0.2) [97].

Exploratory analyses

A specific set of exploratory analyses between hight and patient reported outcomes (QoL, pain and functional independence) were performed as part of LIAISE. Signifcant positive correlations were observed between height z-score and QoL in patients 5–17 years old, as measured by patient-reported QoLISSY and PedsQL total scores (QoLISSY: 0.394 [p≤0.01]; PedsQL: 0.266 [p≤0.01]). Similarly, height was signifcantly positively correlated with the QoLISSY total score in this group. Also in patients aged ≥18 years results from these exploratory analyses identifed height z-score to be a significant driver of the QoLISSY total score (p<0.05), as well as the PedsQL total score (p<0.05). A signifcant positive correlation between height z-score and the total score of the WeeFIM questionnaire was identifed among patients aged 5–17 (0.351 [p≤0.01]). The results show that functional independence is correlated to height and height Z-score (low to moderate associations between WeeFIM® overall total score, the self-care domain score and the mobility domain score, and height and height Z-score), suggesting that patients' functional independence tended to improve with increased height [97].

Safety

This is an epidemiological, non-interventional study and did not solicit any safety data collection or reporting from subjects or Investigators, nor intended to collect and prospectively follow-up information about the use of a specific medicinal product and potential related safety.

7.3 Clinical Safety Pooled data

Safety data from six interventional studies are included in this application: 111-202 (2.5, 7.5, 15 or 30 µg/kg vosoritide); 111-205, 111-206 and 111-208 (15 or 30 µg/kg vosoritide), and 111-301 and 111-302 (15 µg/kg vosoritide).

The Phase II and III clinical studies were considered generally similar in design to justify pooling of the data to facilitate evaluation of long-term safety of vosoritide on the maximum number of ACH subjects exposed to vosoritide for the longest duration. Three pooled populations were defined to evaluate the safety profile of vosoritide in ACH subjects:

- All Treated population (pooled) – all ACH subjects treated with daily vosoritide irrespective of the age or dose received (N=164)
- Maximum 15 µg/kg population - all ACH subjects treated with at least one dose of, and no higher than, vosoritide 15 µg/kg daily (N=148)
- Pure 15 µg/kg population - all ACH subjects aged ≥5 years treated exclusively with vosoritide 15 µg/kg daily (N=131)

7.3.1 Adverse events

In the pooled safety data population (all treated population) 82.3% of the patients experienced at least 1 AE during the studies with an overall exposure adjusted event rate of 79.01 AEs/person-year. SAEs were experienced by 9 (5.5%) subjects; none were considered related to study treatment or led to study drug or study discontinuation [126].

The majority of AEs reported during the studies were Grade 1 (mild) or 2 (moderate), with 10 (6.1%) subjects in the All Treated group reporting a Grade 3 (severe) event.

No Grade 4 AEs or deaths were reported. A total of 3 (1.8%) subjects discontinued treatment due to an AE, including 1 subject treated with 30 µg/kg due to Wolff-Parkinson syndrome (Grade 1), and 2 subjects treated with 15 µg/kg due to AEs of procedural anxiety (Grade 1) and transaminases increased (Grade 2) each [126].

A total of 10 serious AEs (SAEs) were reported in 9 subjects across all Phase 2 and 3 vosoritide studies. These events are reported as sleep apnoea syndrome [2 subjects], tonsillar hypertrophy, thyroglossal cyst, syringomyelia, influenza,

adenoidal hypertrophy, radius fracture, otitis media chronic, generalised tonic clonic seizure). The types of events reported as SAEs were consistent with common childhood illnesses or with events expected in children with ACH. None of the SAEs were assessed as related to study treatment or led to study drug discontinuation [126].

Detailed safety information for all studies are found in Appendix E.

7.3.2 Conclusion

Vosoritide treatment has safe and persistent growth-promoting effects in children with ACH treated daily for over 3, 5 years. The results of the Phase III RCT and extension study (111-301/111-302) of vosoritide supports the positive effect of treatment on AGV and height Z-score demonstrated in Phase II trials with up to 7.5 years follow up.

7.4 Comparative analyses of efficacy and safety

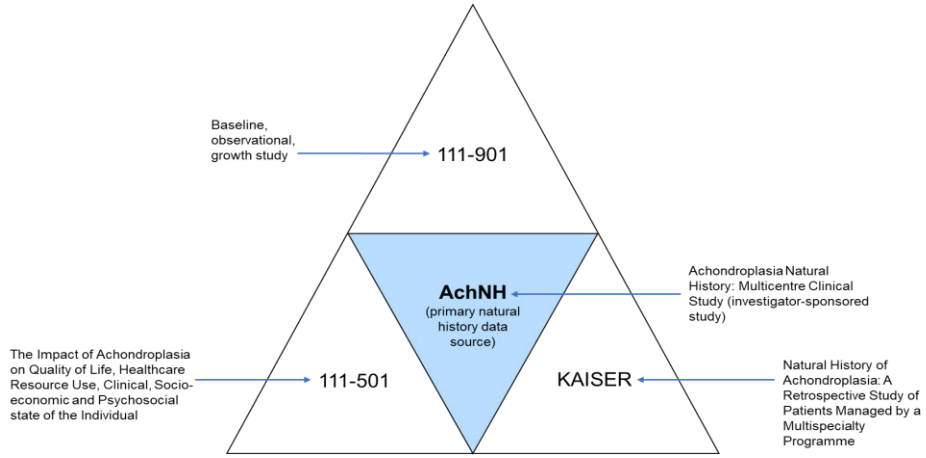
7.4.1 Data of natural history

The durability of the treatment effect with vosoritide was assessed by comparing the results of extension clinical studies (111-205 and 111-302) with natural history data from ACH.

The package of NH data sources used as external controls includes contemporary, prospective and retrospective observational studies conducted in North America and Europe across a broad pediatric age range, namely:

- ACH Natural History: multicenter clinical study (Principal Investigator Julie Hoover-Fong, MD, PhD) (hereafter referred to as the AchNH study)
- BioMarin's baseline, observational, growth study (111-901)
- The Impact of ACH on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial State of the Individual (study 111-501/LIAISE)
- Natural History of ACH: A Retrospective Study of Patients Managed by a Multispecialty Program (Principal Investigator Ericka Okenfuss, MS, LCGC) (hereafter referred to as KAISER).

Figure 34. Data of natural history used for comparative analysis



AchNH: ACH natural history multicentre clinical study.
Source: BioMarin (2020) Natural History Integrated Analyses Report, Figure 1.1 [33]

Table 13. Overview of natural history sources

Study	Number of sites	Objective	Study population	Type of data collection	Protocol date	Date data received/ data cut	Patients enrolled
AchNH	4	Observational investigator-sponsored study to characterize growth (height, height velocity, weight, and BMI) in ACH	All prior or current clinical patients of all ages at participating study sites with a diagnosis of ACH	Retrospective from medical charts	Dec 2015	21 Nov 2019	1374
111-901	27	Observational to collect baseline growth measurements on patients being considered for subsequent enrolment in 111-202, 111-301 and 111-206	Pediatric patients with ACH from birth to ≤17 years of age	Prospective; observation period of up to 7 years	Dec 2011	30 Nov 2019	352
111-501	11	Observational, track impact on QoL, clinical burden, healthcare resource use, socio-economic burden, and psychosocial burden of ACH	ACH patients of all ages at participating European study sites	Retrospective from medical charts	Jan 2017	01 Nov 2019	128
KAISER	1	Observational investigator-sponsored study to determine baseline characteristics and natural history in ACH	ACH Subjects in Kaiser Permanente, Northern California Skeletal Dysplasia Program	Retrospective from medical charts	June 2016	21 July 2019	114

Source: BioMarin Natural history integrated analyses report, 2020 [33]
Abbreviations: AchNH, ACH natural history multicentre clinical study; BMI, body mass index; QoL, quality of life

7.4.1.1 Matching of subjects to form the Natural History Control arm

The comparative analyses included comparisons between the vosoritide group (consisting of several treatment groups from studies 111-202/205 and 111-301) and the external control group (untreated ACH subjects from the NH sources). The subjects included in the external control group for most comparative analyses were selected by a sex and age matching process to each subject in the vosoritide group. [33]

Sex and age are the most critical factors when tracking the development of skeletal growth as evidenced by CDC growth charts as well as published height data in the ACH population, which are all summarized by sex and age [5, 34, 35, 122, 127].

The external control group included the subset of subjects from the NH data source who had a confirmed diagnosis of ACH, available sex data, and at least one standing height assessment available that was taken at a known age. Post-event height assessments were excluded for those subjects who received vosoritide or growth hormone, or underwent limb lengthening surgery. Each subject was matched by sex and age to the vosoritide subject. If subjects had height assessments at different ages, this primary step resulted in subjects from the NH source being matched to more than one subject in the vosoritide group. When this occurred, subjects from the NH source were randomly assigned to one sex and age group of the vosoritide subjects, with an equal probability. Similarly, if multiple subjects in the vosoritide group had the same sex and age, the same set of subjects from the NH source were matched to all of the vosoritide subjects. When this occurred, the subjects from the NH source were assigned to one of the vosoritide subjects, with equal probability. The matching algorithm resulted in each subject in the vosoritide group being matched to a unique group of subjects from the NH source with a different number of NH subjects in each matched group. [33]

The resulting age- and gender matched NH cohort formed the **primary natural history population** in the comparative analyses

7.4.2 Method of synthesis - Statistical Methods for Comparative Analyses

7.4.2.1 Primary Analysis:

• 5-Year Cross-Sectional Comparative Analysis (TTest)

The 5-Year cross-sectional comparative analyses compared height between the vosoritide arm and the Natural History (NH) Control Arm. The difference between the height of each subject from the Vosoritide arm and the average height of subjects who were matched to this subject from the NH Control Arm was calculated at Year 5 using the corresponding analysis population at Year 5 (i.e., Month 60). Similarly, the difference was calculated at Baseline using the corresponding analysis population at the baseline. The difference between the difference of height at Year 5 and that at Baseline was calculated and tested by using one sample t-test. SAS Proc TTest was used to estimate the mean difference between the difference of active arm versus control arm at Year 5 and that at Baseline with 2-sided p-value and 95% confidence interval (CI). [33]

7.4.2.2 Supportive Analyses:

• 5-Year Cross-Sectional Comparative Analysis (ANCOVA)

For the same analysis populations for cross-sectional comparative analysis used for TTest, cross-sectional analyses at Year 5 and Baseline also used an ANCOVA model that included the fixed-effects of treatment (active arm vs. NH arm) and indicator variables for the matching based on sex and age combination. SAS Proc Mixed was used to estimate the least square (LS) mean difference between the active arm versus control arm with 2-sided p-value and 95% CI. Both analyses (t-test and ANCOVA) were performed for the endpoint height Z-score. [33]

• 5-Year Longitudinal Comparative Analysis

The 5-Year longitudinal comparative analysis compared changes from baseline at Year-5 (i.e., Month 60) for height and height Z score between the Vosoritide arm and the NH Control Arm. The 5-Year longitudinal comparative populations analysis was used. The change from baseline in height of each subject from the Vosoritide arm and the average of change from baseline in height of subjects who were matched to this subject from the NH Control Arm was calculated. The difference between the change from baseline from Vosoritide arm and that from NH Control Arm was calculated and tested by using one sample t-test. Similar summary statistics used for the 5-Year cross-sectional comparative analysis was used for 5-Year longitudinal comparative analysis. Analysis of change from baseline in height and height Z-Score was also performed using an ANCOVA model that included the fixed-effects of treatment (active arm vs. NH arm) and indicator variables for the matching based on sex and age combination. SAS Proc Mixed was used to estimate the LS mean difference between the two arms with 2-sided p-value and 95% CI. [33]

• 4-Year Cross-Sectional Comparative Analyses

Similar cross-sectional analyses that were done for the 5-Year cross-sectional comparative analysis were also conducted for the 4-Year cross-sectional comparative analysis using the 4-Year cross-sectional comparative analysis population (i.e., at Year 4 and at Baseline). [33]

• 4-Year Longitudinal Comparative Analysis

Similar longitudinal analyses that were done for the 5-Year longitudinal comparative analysis were also conducted for the 4-Year longitudinal comparative analyses using the 4-Year longitudinal comparative analysis population. [33]

• 2-Year Longitudinal Comparative Analysis

The **2-**Year longitudinal comparative analysis compared treatment effects between vosoritide arm and NH Control Arm for the change from baseline in AGV, height, and height Z-Score at Year 2 (i.e., Month 24) using the 2-Year longitudinal comparative analysis population. Analysis of change from baseline in AGV was performed using an ANCOVA model that included the fixed effects of treatment (active arm vs. NH arm) and indicator variables for the matching based on sex and age combination, baseline AGV and height Z-Score. Similar analysis was also performed for endpoints height Z-Score

and height. Within this analysis is included a comparison for AGV, height, and height Z-Score at Year 1. Sensitivity and other supportive analyses were conducted in a similar fashion. [33]

Table 14. Summary of primary and supportive comparative analysis

Type of analysis[a,b]		Analysis Population for Vosoritide Group	Analysis population for External Control Group
Primary	**5-year cross-sectional** analysis on height at 5-years follow up between vosoritide group and external control	Cohort 3 of 111-202/205 *(subjects who received 15 µg/kg)*	Primary NH source[c]
Supportive	**5-year longitudinal** analysis on height at 5-years follow-up between vosoritide group and external control	Cohort 3 of 111-202/205 *(subjects who received 15 µg/kg)*	Primary NH source[d]
	5-year cross-sectional and **longitudinal** analysis on height at 5-years follow up between vosoritide group and external control	Cohorts 1, 2 and 3 of 111-202/205 *(including all data for subjects who were assigned to receive 2.5 µg/kg, 7.5 µg/kg or15 µg/kg, respectively)*	Primary NH source[c]
	4-year cross-sectional and **longitudinal** analysis on height at 4-years follow up between vosoritide group and external control	Cohorts 1, 2 and 3 rebaselined of 111-202/205e *(only including data forsubjects while receiving 15 µg/kg)*	Primary NH source[c]
	4-year cross-sectional and **longitudinal** analysis on height at 4-years follow up between vosoritide group and external control	Cohort 4 of 111-202/205 *(subjects who received 30 µg/kg)*	Primary NH source[c]
	2-year longitudinal analysis on AGV at 2-years follow up between vosoritide group and external control	Cohort 1, 2, 3 of 111-202e *(only including data for subjects while receiving 15 µg/kg)* combined with vosoritide group of 111-301 *(subjects who received 15 µg/kg)*	Primary NH source

AGV, annualized growth velocity; NH, natural history.
a Cross-sectional analyses compared the difference between height at Year 5 or Year 4 follow-up and at baseline between the vosoritide group and the external control group. All analyses were repeated for height Z-score.
b Longitudinal analyses compared the change from baseline in height at Year 5 or Year 4 (all analyses were repeated for height Z-score) or the change from baseline in AGV at Year 2 (all analyses were repeated for height and height Z-score).
c The cross-sectional analysis was repeated using the supportive pooled NH sources. Supportive pooled NH sources were used for cross-sectional analyses only because there were not sufficient subjects from the external control group to match with subjects in the vosoritide group
[d] The longitudinal analyses were repeated using a covariate adjusted model without matching, therefore, sufficient data was available for analyses also using the supportive pooled NH sources.
[e] Subjects in Cohorts 1 and 2 sequentially dose-escalated to 15 µg/kg during 111-202; these subjects were re-baselined to the start of receiving 15 µg/kg vosoritide for the purposes of the analyses.

7.4.2.3 Handling of Missing Data

Missing data is not imputed for subjects from the active control arm. Since assessments are not conducted on a regular basis for the NH data sources, there are no missing visits as in a clinical trial setting. Therefore, no imputation was conducted. [33]

7.4.3 Results from the comparative analysis

The pre-specified main analysis was a cross-sectional analysis over a period of 5 years with the objective of comparing the variation between the size at baseline and at year 5 between Cohort 3 of the vosoritide group (15 µg/kg) studies 111-202 and 111-205 compared to the external control group matched by age and sex of the primary source of natural history (AchNH). Supportive analyzes and sensitivity analyzes were performed to assess the strength of the results.

7.4.3.1 5-year cross-sectional primary analysis

At baseline, there was a statistically significant difference in height between the patients in the vosoritide group and the untreated ACH patients in the external control from the matched (see section 7.4.1.1) primary natural history population [redacted] This was principally due to one patient in Cohort 3 who had undergone limb lengthening prior to entry into the vosoritide study. [33]

At Year 5, there was a statistically significant difference in height between the two groups [redacted] in favour of vosoritide, which remained significant after adjusting for differences at baseline [redacted] (Figure 35). These results were consistent when using a sex and age matched external control group from the pooled other natural history sources [redacted] [33]

Figure 35. Change in mean height from baseline to Year 5 (cross-sectional)

[redacted]

7.4.3.2 Supportive and sensitivity analyses

The supportive 5-year longitudinal analysis, which compared change in height from baseline at Year 5 between patients in 111-202/205 who received vosoritide 15 µg/kg to sex- and age-matched patients from the primary natural history descriptive population with 5 years follow-up, showed an estimated mean difference in height gain between patients in the vosoritide group and the external control of untreated ACH patients of [redacted] cm in favour of vosoritide. The sensitivity analysis of covariance (ANCOVA) without matching, and consequently a larger external control group (N=217) including covariate-adjustment for baseline height, sex and age, provided consistent results. [33]

The height gain increase observed over 5 years in patients treated with 15 µg/kg vosoritide over the external control was consistent with [redacted] multiple of the gain in height observed in pivotal study 111-301 over a 1-year period compared with the placebo control, which in turn was consistent with the comparison of the 111-301 vosoritide group versus the sex- and age- matched external control. These results suggest that the positive effect on growth with vosoritide is maintained year-by-year. [33]

The conclusions of the primary cross-sectional analyses were confirmed by the multiple supportive and sensitivity analyses, irrespective of statistical analysis method used or various subsets of patients selected from the natural history sources (primary or supportive pooled). [33]

7.4.3.3 Conclusion

Comparative analyzes, carried out between patients treated with vosoritide at 15 µg/kg during clinical studies 111-202 and 111-205 and patients in natural history studies of the disease, demonstrated the long-term effect of treatment with vosoritide with a significant difference in height gain of [redacted] between the patients treated and the patients not treated with vosoritide in 5 years compared to baseline.

The results of the phase III (111-302) and phase II (111-205) extension studies also provide further evidence of the long-lasting therapeutic effect of vosoritide.

7.5 Extrapolation of relative efficacy

7.5.1 Potential Height at age of 16 years

Extrapolation was performed to understand the potential impact of vosoritide treatment on final adult height. Final adult height was estimated for the 10 subjects from Cohort 3 of Study 202/205 whose height at age 16 years was determined by extrapolation and mean results were compared to the mean height of 16-year-olds from the Primary NH descriptive Population.

Different assumptions were applied for the extrapolated growth ranging from the best-case scenario that subjects continued to grow at the same rate at the time of the data cut to the worst-case scenario that the subjects grew no more after the time of the data cut off. In the best-case scenario, individual subjects' height was extrapolated from the last height assessment at the data cut-off to the time when the subject reaches 16 years of age, based on Active AGV (Active AGV assumes that subjects continue to grow at the same AGV observed on vosoritide). There was a mean difference of [redacted] compared between subjects in the vosoritide group from Cohort 3 to the external control (Figure 36). In the worst-case scenario where the subjects no longer grew (last observed carried forward [LOCF]), there was still a difference of [redacted] compared between subjects in the vosoritide group to the external control.

Figure 36. Extrapolated Near Final Adult Height at Age of 16 Years Old (Analysis Population: 111-202/205 Cohort 3 and Primary NH Descriptive Population)

[redacted]

Source: Based on 111-202/205 data cut-off at 30 November 2020. Efficacy Update Report: Durability of Vosoritide Treatment Effect. Dated 17 March 2021 and submitted as part of the EMA filing.

8. Health economic analysis

8.1 Model

The model structure was informed by the review of relevant clinical guidelines, an economic Systematic literature review (SLR), and existing economic studies in ACH. No existing economic models of ACH were identified. Consequently, the model structure was designed with consideration of the biological action of vosoritide, consideration of economic models in related restricted growth conditions, and expert clinical advice.

Vosoritide has been shown to promote sustained improvements in bone growth during childhood and adolescence, which manifests as increased growth velocity and height z-score compared to age and sex- matched untreated individuals with ACH [128]. In post-hoc analysis of the vosoritide clinical trial datasets, height deficits have been shown to correlate with impaired quality of life and activities of daily living [36]. This finding was supported by data from the LIAISE study which indicated a correlation between height and patient functionality and quality of life [109, 129].

The effects of ACH are experienced over patients' lifetimes. The experience of each patient depends on the anthropometrics achieved by the individual during childhood and the complications that occur throughout life. An **individual simulation model** was therefore judged to be the most appropriate modelling approach, given the heterogeneity between patients and the importance of patient characteristics on the individual disease course, the existence of several potential interacting factors (e.g., foramen magnum stenosis and decompression surgery) and the need to track patient history.

Individual simulation models involve sampling first-order parameter values (e.g., patient characteristics, height, weight etc.) and second-order parameter values (e.g., model inputs, efficacy, patient utility).

The model is constructed both in the worksheets, to facilitate calculations verification and transparency, and in Visual Basic for Applications (VBA), to improve model efficiency and reduce computational times. Both platforms are constructed identically and validated to generate identical results[1].

8.1.1 Overview of model structure

The economic evaluation is undertaken using an **individual simulation model**, which captures the impact of reduced stature on QoL and the incidence of complications related to ACH **over the lifetime** of the patient. An individual simulation model is needed to capture the varying disease courses across people with ACH and the sequalae of complications.

The CEM captures the impact of both reduced stature and complications associated with ACH on QoL. The CEM considers costs falling on the health care sector for treatment with vosoritide and for the management of complications associated with ACH that are mitigated through treatment with vosoritide. Growth is simulated throughout childhood according to the natural variation observed in children with ACH and the impact of treatment with vosoritide. The impact of reduced stature on QoL is modelled using the simulated height of the patient and evidence on the impact of reduced stature on QoL from a large, English population dataset [40]. The impact of complications associated with ACH on QoL are also captured [40].

[1] An important note to understand the excel model correctly is that the 'Efficacy Calc', "VosoritideCalc", and "ComparatorCalc" tabs only displays the calculations for one of the 1000 simulated patients – it does not represent a summary of the entire simulated cohort. The VBA macro that is activated by the button "Run deterministic simulation (sheets)" will update the "EfficacyCalc", "VosoritideCalc", and "ComparatorCalc" sheets for the 1000 simulated patients, one at the time, and for each patient the relevant resulting data will be exported to the "ResultsCalc" sheet. The average results for the entire simulated cohort are calculated in the "ResultsCalc" sheet.

The incidence and sequalae of the most important complications are modelled both under BSC and after treatment with vosoritide. The likelihood of complications is modelled as a function of the extent of growth retardation. Consequently, complication risks vary between patients and according to their treatment status.

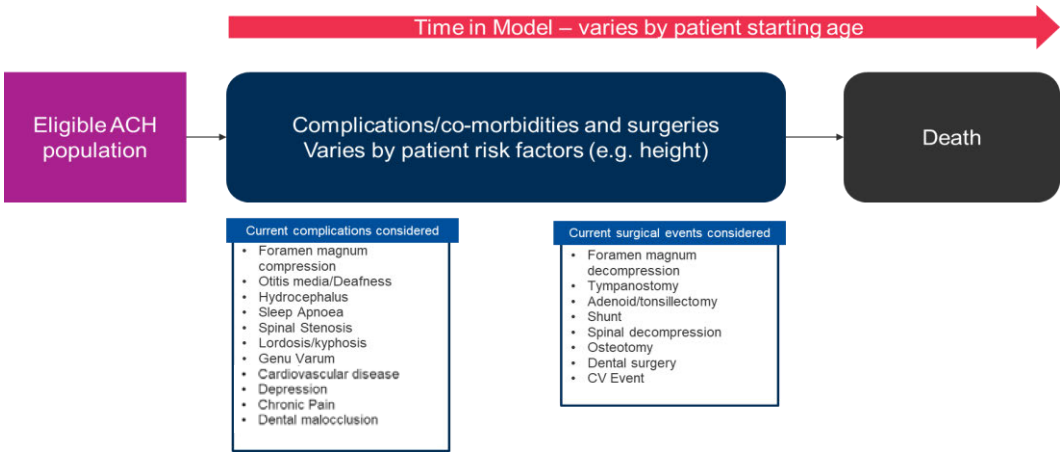
Patients enter the model aged 2 years; a baseline patient profile is generated for each patient; and each patient's lifetime disease course (up to age 100) is then individually simulated both with and without treatment with vosoritide. The baseline height, weight and body proportion for each patient is simulated from ACH natural history growth curves based on the Natural History Integrated Report data, produced by internal analysis conducted by BioMarin [33].

The model is run for 1,000 patients and averages the costs and benefits across simulations with and without treatment to determine incremental costs and outcomes, and an incremental cost-effectiveness ratio (ICER). The model uses a **cycle length of 1 year**.

A half-cycle correction is not implemented in the base case. The incidence of complications is applied at the start of each year in the simulation. The model conservatively calculates the impact of treatment with vosoritide at the end of each year of treatment. The impact of applying a half cycle correction can be examined in sensitivity analysis and generates a modestly improved ICER for vosoritide.

The model tracks a patient's anthropometric measures and events that occur over time as shown in Figure 37. Patients are exposed to various event risks as they progress through the model. For each yearly cycle, the model calculates the patient's change in height, weight, and proportionality. The model considers the benefit of increased height, the impact of any one-time events (e.g., surgery) and the presence of any new or existing complications. When a patient develops a complication, the model increases the patient's annual care costs, lowers their QoL, and adjusts their survival risk. The effects of complications are applied multiplicatively to the risk of death and to QoL.

Figure 37. Schematic of model structure



Abbreviations: ACH, achondroplasia.

The annual risk of complications is a function of patient age and the percentage of average stature height achieved in each cycle. Some complications require surgery, which is assumed to take place in the year of the complication manifesting. Surgery is associated with costs and a detrimental impact on QoL during the relevant year. For some complications requiring surgery and for all complications not requiring surgery, treatment costs are accrued in subsequent years and QoL is reduced. The duration of the longer-term impact of complications varies by complication, reflecting disease aetiology. A lifetime duration is assumed for the majority of complications. Where clinically appropriate, complications also increase the risk of mortality. This is captured by applying a risk ratio to general mortality risk as a function of age and sex derived from Danish National Life Table data [130]. The impact of multiple complications on mortality risk is multiplicative.

The overall model structure, including the impact of reduced stature on QoL, and the impact of the restoration of growth on the rate of complications associated with ACH were discussed and validated at an advisory board meeting with clinical experts from Denmark [131].

Costs and QALYs accrued in each year beyond the first are **discounted at a rate of 3.5% for year 0-35, 2.5% for year 36-70, and 1.5% beyond 70 years**, in accordance with the Danish Finansministeriet's guidelines for economic evaluations [132].

8.1.2 Modelling treatment effect of vosoritide

8.1.2.1 Growth simulation

Growth is modelled on a yearly basis according to the height of the simulated patient at entry into the model. For each year of childhood, the mean AGV and SD are used to determine the AGV for each simulated children according to the centile of their height at entry into the model (patients with a greater height for their age at model entry will experience higher AGV in the model). Data on the distribution of baseline height in children with ACH by age, and the resulting growth curves, were taken from Merker 2018 [5] who reported growth references from a European cohort of children with ACH.

For each simulated patient in the model, the corresponding baseline height and growth curve in the absence of ACH is also modelled, providing age dependent AGV reference values. Growth curves for the average stature population were taken from Danish standardised growth charts for height and weight [133]. In a scenario analysis, WHO standardised growth curves [134] are used in place of the Danish data. Growth trajectory in the absence of ACH was simulated according to the growth curve for the average stature population on the same centile value for their height according to the population distribution.

8.1.2.1.1 Efficacy estimate

Based on the clinical trial data, treatment with vosoritide is assumed to improve AGV. The treatment effect is modelled as percentage recovery of expected AGV (PRAGV). This is defined as the difference between the observed AGV and the expected AGV for a child of that age, sex and birth height with achondroplasia divided by the difference between the AGV for an average stature child and that for a child with achondroplasia of the specified age and sex:

$$PRAGV = \frac{AGV_{obs} - AGV_{ach}}{AGV_{as} - AGV_{ach}}$$

where AGVobs is the observed AGV, and AGVach and AGVas are the AGV expected for a child of that age and sex with achondroplasia and of average stature, respectively. While AGV is age dependent, it is assumed in the model that the PRAGV is independent of age.

In the base case, a PRAGV of 77.28% was assumed based on effectiveness data from Study 111-301 [135]. Treatment with vosoritide was thus assumed to restore 77.28% of the shortfall in AGV for a patient with ACH compared to an average stature person of the same age, sex, and birth height percentile, in the given year of treatment. This estimate of the proportional improvement in AGV attributable to vosoritide is applied in the model for each year a child with ACH receives treatment with vosoritide.

8.1.2.1.2 Durability of treatment effect

The data from Study 111-301 show improvements in growth attributable to vosoritide across the age range of enrolled patients, demonstrating effectiveness at younger and older ages. Duration of follow-up in Study 111-301 is inevitably limited and hence the model applies the assumption that the effectiveness of treatment is maintained whilst children remain on treatment.

In effect, the model assumes that the benefit of vosoritide at each age observed for treatment-naïve children in Study 111-301 will also manifest for children treated with vosoritide in previous years. This assumption is supported by the results of Study 111-302 and Study 111-205. Study 111-302 is the follow-up observational study to Study 111-301 in which patients from both received vosoritide. Data over 48 months demonstrates maintenance of improved AGV observed in the vosoritide arm of Study 111-301 (Section 7.2.1.1). Study 111-205 is a smaller observational study which

will follow 30 patients for at least 5 years. Data to date (data cut-off 25 February 2022) show that improvements in AGV are maintained over observation periods up to 7 years (Section 7.2.2.2).

8.1.2.2 Reduction of complication rates

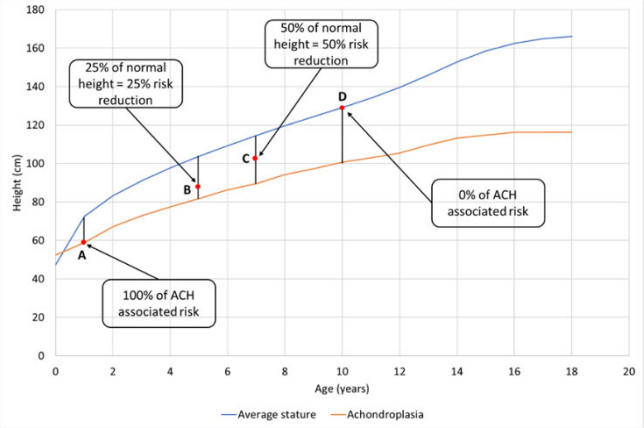
In the model, the increase in bone growth attributable to vosoritide treatment is assumed to reduce the likelihood of complications arising from ACH. Complications included in the model are: Foramen magnum stenosis requiring decompression surgery, Hydrocephalus requiring shunt surgery, Sleep apnoea, Spinal stenosis requiring surgery (laminectomy), Kyphosis and lordosis requiring surgery (spinal fusion), Genu varum (leg bowing), Cardiovascular disease, Depression, Chronic pain, Otitis media, Hearing loss, and Dental malocclusion.

The risk reduction is estimated as the reduction in height difference compared to average stature individuals at the same age, relative to ACH patients without treatment (illustrated schematically in Figure 38 and Figure 39).

Figure 38 shows the height of a sampled individual with either average stature or ACH over time. The height difference at ages 1, 5, 7 and 10 is shown using vertical lines, with red marks indicating hypothetical examples of height improvements at respective age achieved while on vosoritide treatment. For each timepoint, the percentage of normal height is calculated as:

$(Height_{VOS} - Height_{ACH}) \div (Height_{AverageStature} - Height_{ACH})$

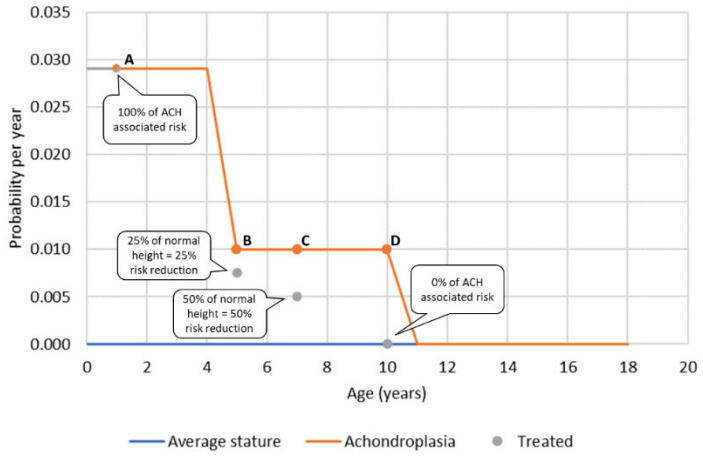
Figure 38. Risk reduction based on percent of average stature height



Abbreviations: ACH, achondroplasia.

Figure 39 then illustrates the exemplified impact on the probability of a complication by age (for which the assumed rate in the general population is zero). The equivalent points are marked using letters in Figure 38 and Figure 39. At age 1 (denoted by letter A in the figures), the patient has not achieved any height improvement and therefore suffers 100% of the annual risk of the complication (i.e. 100% x 0.029). At ages 5 and 7 (marked by the letters B and C in the figures, respectively), the patient has achieved 25% and 50%, respectively, of the difference between the mean height for patients with ACH and average stature and will gain a reduction in annual risk of the complication of 25% (75% x 0.01) and 50% (50% x 0.01), respectively. Similarly, at age 10 (marked by letter D in the figures), the patient has achieved 100% of normal height, and therefore, suffers 0% of the risk of the complication (0% x 0.01).

Figure 39. Illustrative example of reduced risk of complications



Abbreviations: ACH, achondroplasia.

For most complications modelled, the risk in the general population is above zero. In these cases, the proportionate reduction in the risk of the complication is relative to the value in the general population, rather than zero. Hence the risk for a patient at point D on Figure 38 would be that of the general population for these complications.

This approach to estimate the reduction of the risk of complications upon vosoritide treatment was discussed and validated by clinical experts in the advisory boards organised by BioMarin [131]. The advisors agreed that while there may not be a causal relationship between growth and risk reduction, it is likely that the underlying mechanism of action of vosoritide will have impact on bone growth as well as on the risk of ACH complications, and that the extent of restored growth at a given timepoint is the best available proxy for the accumulated systemic effect of the vosoritide treatment.

8.1.2.3 Baseline risk of complications

For the included complications, the model considers the incidence above the rate expected in the general population. The primary source of data is the LIAISE study [10]. As described in section 7.2.3.2, this study was commissioned by BioMarin and enrolled 195 patients from six European countries (Austria, Denmark, Italy, Germany, Spain and Sweden). The study assessed the impact of ACH natural history, on QoL, clinical burden (including complication rates), healthcare resource use, socio-economic burden (educational and employment) and psychosocial burden. In the base case, the LIAISE study was prioritised in the estimation of event rates, as it was considered the most relevant source to inform complication rates for the ACH population in Denmark.

In LIAISE, health care resource use data were collected retrospectively from patient medical records, and patients were required to have a minimum of 5 years of medical records prior to recruitment. At enrolment, where available, data were collected up to 9 years previously. Nine patients were not included in the analysis of health care resource use and complications due to missing medical records. Of the remaining 186 participants, 181 (97.3%) had records over 5 years or more, and 87 (46.8%) had medical records extending back 10 years or more. Event rates for complications were calculated as the number of events divided by the total number of historical years.

Table 15 reports the number of participants in LIAISE experiencing the complications included in the model, together with event rates, by age subgroup. Most participants in LIAISE were aged 15 years or under (52%). Consequently, participants in older age groups were pooled for the purpose of estimating resource use and complication rates. A pragmatic decision was made to pool the age groups 16–20, 21–30 and 31–40 into one group (16–40), and to pool the age groups 41–50, 51–60 and over 60 into a single over 40 age group.

Data on decompression surgery (DCS), shunt insertion, tympanostomy, spinal stenosis, lordosis/kyphosis, and limb lengthening refer to the number of patients receiving a surgical intervention for the complication. Data on obstructive sleep apnoea, genu varum, cardiovascular disease (CVD) events, chronic pain, and dental overcrowding refer to patients with a recorded diagnosis. Data on hearing loss refer to the number of participants who received an audiological

assessment. Event rates were calculated by dividing the number of events by the total number of observation years in that age group and are expressed as rates per 100 person years.

Table 15: Rates of complications observed in LIAISE after amalgamation of age subgroups

Complication	Complication rate, by age subgroup n /(rate per 100 person years)				
	0–4 (PHY=431.0)	5–10 (PHY=494.9)	11–15 (PHY=291.8)	16–40 (PHY=704.3)	>40 (PHY=239.5)
Foramen magnum stenosis*	11 (2.6)	6 (1.2)	0	1 (0.1)	0
Shunt insertion	5 (1.2)	0	0	1 (0.1)	0
Sleep apnoea	24 (3.9)	8 (1.6)	0	1 (0.1)	1 (0.4)
Spinal stenosis/ nerve decompression*	3 (0.7)	0	1 (0.3)	2 (0.3)	1 (0.4)
Kyphosis/lordosis*	0	3 (0.6)	3 (1.0)	1 (0.1)	6 (2.5)
Genu varum/vagum	17 (3.9)	6 (1.2)	2 (0.7)	2 (0.3)	0
CVD event	4 (0.9)	2 (0.4)	0	5 (0.7)	0
Depression	1 (0.2)	2 (0.4)	2 (0.7)	1 (0.1)	1 (0.4)
Chronic neck/ back pain	3 (0.7)	2 (0.4)	1 (0.3)	6 (0.9)	2 (0.8)
Tympanostomy**	10 (2.3)	9 (1.8)	1 (0.3)	0	0
Hearing loss	17 (3.9)	23 (4.6)	2 (0.7)	2 (0.3)	2 (0.8)
Dental overcrowding	2 (0.5)	6 (1.2)	2 (0.7)	1 (0.1)	0
Limb lengthening	2 (0.5)	13 (2.6)	18 (6.2)	15 (2.1)	0

**Event rates indicate surgery for the respective condition. **Includes myringotomy.*

Abbreviations: CVD, cardiovascular disease; LIAISE, Lifetime Impact of Achondroplasia Study in Europe; PHY, patient historical years.

Source: BioMarin 111-501 Exploratory Analyses Report, 2020 [10]

Age-dependent incidence rates in the general population for the complications were derived from literature sources (Table 16). For foramen magnum stenosis requiring decompression surgery; hydrocephalus requiring shunt surgery; kyphosis/lordosis; and leg bowing requiring surgery, the incidence in the general population was assumed to be zero.

Table 16. Rates of complications in general population as applied in the CEM

Complication	Annual complication rate, by age band		Source
Obstructive sleep apnoea	0<30	0.0000	Duran et al, 2001 [136]
	30<39	0.0018	
	40<49	0.0058	
	50<59	0.0071	
	60<69	0.0073	
Spinal stenosis requiring surgery	All ages	0.000097	Jansson et al, 2003 [137]
CVD	0 < 16	0.0000	Bhatnagar et al. 2016, Figure 5 [138]
	16 < 45	0.0014	
	45 < 65	0.0040	
	65 < 75	0.0104	
	≥ 75	0.0020	
Depression	0 < 12	0.0000	Pratt 2014, Figure 1 [139]
	12 < 18	0.0097	
	18 < 40	0.0008	
	40 < 60	0.0012	
	≥ 60	0.0000	
Chronic pain	0-8	0.000	Raftery et al, 2011 [140]
	9-26	0.006	
	27-39	0.001	
	40-49	0.002	
	45-59	0.002	
	60-69	0.001	
	70+	0.001	
Tympanostomy	2-8	0.004	Parker et al, 2016 [141]
	9+	0.000	

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Hearing loss	<1	0.0012	Monasta et al. 2012, Table 3 [142]
	1 < 14	0.0002	
	≥ 14	0.0005	
Orthodontic treatment	<10	0.0000	Breistein et al. 1998 [143]
	10-16	0.0052	
	>16	0.0000	

8.1.2.4 Limb lengthening

Utilisation of limb lengthening surgery differs between health care settings. As confirmed by consulted clinical experts, it is very rarely performed in Denmark (0-5%). In the base case analysis, limb lengthening was therefore excluded.

8.1.2.5 Obesity

The limitations on activities of daily living are likely to be the cause of greater levels of obesity in patients with ACH compared to the general population. Consequently, an improvement in height and proportionality is expected to be accompanied by a reduction in obesity. An improvement in obesity was modelled in a scenario analysis. Weight as a function of age, sex and birth percentile was derived from World Health Organization (WHO) growth charts for the average stature population [134], and from Hoover-Fong for patients with ACH [34]. The impact of treatment with vosoritide was modelled as a percentage reduction in the difference in annual weight gain between the average stature population and patients with ACH. A 77% reduction was modelled to align with the modelled impact of treatment with vosoritide on AGV. Patients were considered obese if their body mass index (BMI) exceeded 40 as calculated using the Quetelet formula [144]. Obese patients accrued additional costs, a reduction in QoL and raised mortality.

8.1.2.6 Mortality

The following complications were assumed to increase mortality: **foramen magnum stenosis** (requiring surgery), **obstructive sleep apnoea**, **spinal stenosis** (requiring surgery), **CVD**, **major depression**, and **chronic pain**. Increased mortality arising from complications was captured by applying a SMR to the adjusted age- and sex-specific probability of death. A multiplicative approach was applied to the impact of multiple complications. Table 17 reports the SMRs, source and duration of impact for each relevant complication. The remaining complications were assumed to have no impact on mortality. Only the long-term impact of complications on mortality was considered; any elevated mortality risk from surgical procedures to address complications such as hydrocephalus or genu varum was ignored. Evidence suggests that these risks are small in an otherwise healthy ACH population [145]. Elevated mortality was assumed for the lifetime following incidence of the complication for each complication except foramen magnum stenosis. The increased risk of mortality associated with foramen magnum stenosis was assumed to manifest for four years after birth (Table 17).

Prior to consideration of complications, age and sex specific mortality rates were derived from Danish life tables for 2021 [130] As CVD complications were explicitly modelled, the underlying all-cause mortality rates were adjusted to net out the impact of CVD complications[2]. The adjustment was made by applying the following formula.

$$Padj = Praw/(1 + prev * (SMR - 1))$$

Where Padj is the adjusted probability, Praw is the unadjusted probability, prev is the prevalence of CVD in the relevant age and sex subgroup, and SMR is the standardised mortality ratio for CVD. The resulting probabilities represent the

[2] Mortality derived from lifetables includes the impact of co-morbidities. Hence when a particular disease is modelled separately, the determination of mortality through the application of a SMR to all-cause mortality will double count the impact of that disease. For relatively rare conditions, the impact of this will be negligible and can be ignored. For common conditions, such as CVD, the impact will not be negligible. As the vosoritide model explicitly captures the impact of CVD, it was important to adjust all-cause mortality for the contribution of CVD prior to applying an SMR to patients developing CVD in the model.

risk of death for people without CVD. The model switched to unadjusted mortality rates when CVD complications were excluded from the analysis.

Table 17. Mortality risks associated with complications

Complication	SMR	Duration	Source
Foramen magnum stenosis	1.5	4 years*	Assumption
Obstructive sleep apnoea	1.54	Lifetime	Xie, 2017 [146]
Spinal stenosis	1.77	Lifetime	Poorman, 2018 [147]
CVD	1.93	Lifetime	Ford, 2005 [148]
Depression	1.52	10 years	Cuijpers, 2014 [149]
Chronic pain	1.52	Lifetime	Smith, 2018 [150]

**Assumed duration of four years from birth*
Abbreviations: CVD, cardiovascular disease, SMR, standardised mortality ratio.

8.1.2.7 Mortality risks associated with obesity

The impact of reduction in obesity through improved AGV achieved with vosoritide was modelled in a scenario analysis. In this analysis, obesity was associated with increased mortality. Data on the impact of obesity on mortality were taken from a meta-analysis [151]. The mortality increase was modelled as an SMR applied to the baseline mortality risk dependent on the level of obesity.

Table 18. Impact of obesity on mortality modelled in scenario analysis

BMI range	SMR
Up to 30	1.00
>30 to 35	1.04
>35 to 40	1.29
>40 to 45	1.74
Over 45	2.49

Abbreviations: BMI, body mass index, SMR, standardised mortality ratio.

8.1.3 Validation

8.1.3.1 Internal validation

A systematic validation of the model was undertaken by an external modeler. This included cell by cell checking, verification of formulas and implementation, logical checks, assessment of the consistency of results to changes in input parameters, and a full audit of model inputs. The model incorporates a check to ensure that outputs produced by the Visual Basic for Applications (VBA) implementation of the model match those from the Microsoft® Excel sheets based implementation.

8.1.3.2 External validation

External validation of the modelling approach, clinical and health economic inputs and model outcomes was conducted in a global advisory board, which was organised and funded by BioMarin and conducted on 20 and 21 December 2021 [152]. Expert attendees at the meeting included three clinicians' expert in the treatment of ACH patients and one health economic expert.

The experts considered the modelling approach and structure to be appropriate to capture the clinical events and costs associated with ACH patients over a lifetime. There was agreement that patient baseline characteristics, including age, gender and height were important factors in determining the outcome from treatment with vosoritide.

The experts emphasised that many patient characteristics and complications experienced by ACH are related to each other. The experts expect variation in treatment effect based on age of starting treatment with potentially high and low responders and acknowledged the variation in annualised growth velocity by age in ACH and average stature populations. The experts accepted the assumptions related to growth velocity < 5 years and > 15 years were reasonable and mentioned data availability to inform these ages.

Using height as a surrogate outcome to model a reduction in complication incidence was not accepted for all complications. The experts agreed that for some complications, this would be appropriate but for others (including FMS) this assumption is not supported by evidence. The durability of response was accepted by all experts at the meeting. The expert suggested recently published studies to inform ACH patient weight.

The experts agreed vosoritide was not associated with any serious adverse events. The experts were also supportive of the approach taken to model non-causal health-related quality of life and considered it reasonable.

For complications incidence, the experts provided insight into current studies to inform spinal stenosis, kyphosis and leg-bowing, obstructive sleep apnoea (based on clinical opinion), cardiovascular disease, depression, and obesity. The experts informed the meeting of expected outcomes for limb lengthening.

The experts agreed with the approach taken to apply SMRs and indicated support for the Wynn 2007 study as the most robust source for mortality in ACH. The experts offered landmark values for mortality in FMS, which could be used to validate the relative risk (RR) of FMS up to 4 years (which is currently 1.5 [placeholder]). The experts suggested some adjustments to the one-time QALY loss associated with surgeries associated with complications.

On reviewing the model outcomes, all experts agreed that the model was underestimating the FAH outcome of treatment with vosoritide. It was noted that the model outcomes were expected to improve when patient level data from the clinical trial are made available.

Model outputs included survival curves for the incidence of each complication and overall mean life expectancy in the simulated cohort with and without treatment. The incidence of complications was assessed against the underlying data to ensure the model was correctly representing the underlying risk.

Mean life expectancy for patients in the comparator arm was compared with the available evidence to assess the underlying robustness of the model in predicting a key clinical outcome.

Further validation of the model assumptions from a local perspective was obtained in a Danish advisory board undertaken on January 18, 2023 with three Danish clinicians with experience of treatment of ACH patients [131]. There was consensus opinion among the clinical experts that the estimated AGV improvement was plausible, that the assumption of a sustained and uniform treatment effect across ages is a reasonable approach in the absence of long-term data, and that the approach to model reduction in complication risks upon vosoritide treatment was reasonable.

8.1.4 Key model assumptions

The key assumptions applied in the economic analysis are summarised in Table 19.

Table 19. Summary of assumptions underpinning the economic analysis

Parameter	Assumption	Reference
Model structure	An individual simulation model was used to capture the impact on costs, QoL and mortality of the major complications associated with ACH. The structure was considered best placed to capture the impact of treatment on QoL and mortality arising from reductions in complication rates.	Section 8.1.1
Cycle length	A cycle length of one year was considered sufficiently short to capture the impact of treatment on the incidence of complications whilst minimizing model complexity.	Section 8.1.1
Efficacy of treatment	The impact of treatment on complications is assumed to be proportional to the change in height. This assumption is based on the underlying mechanism of action	Section 8.1.2.1

Parameter	Assumption	Reference
	of vosoritide in restoring bone growth and the nature of the complications associated with ACH which arise from restriction of bone growth.	
Duration of effect of treatment	The impact of treatment on bone growth is assumed to be maintained for the full duration of treatment (until cessation of natural growth), based on available evidence and the underlying mechanism of action of vosoritide.	Section 8.1.2.1
Mortality	Reduced life expectancy associated with ACH is assumed to arise from raised mortality risks associated with complications arising from the condition.	Section 8.1.2.6
QoL and height	Improvements in height lead to increases in QoL. The relationship between reduced height and QoL observed in the UK general population reflects the underlying impact of height on QoL.	Section 8.4.2.1
QoL and complications	Complications reduce QoL. The impact of multiple complications is multiplicative.	Section 8.4.2.2
Complications	The incidence rates of decompression surgery, shunt insertion and kyphosis (requiring surgery) in the average stature population is assumed to be zero.	Section 8.1.2.3

Abbreviations: ACH, achondroplasia; CVD, cardiovascular disease; QoL, quality of life; UK, United Kingdom.

8.1.5 Perspective

The CE analysis is made from a Danish societal perspective in the base-case, while the payer perspective is assessed as a sensitivity analysis.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Percentage recovery of annualized growth velocity (AGV)	Vosoritide vs. placebo: Study 111-301 (ITT)	77.28%	The treatment effect is modelled as percentage recovery of expected AGV (PRAGV). The PRAGV is used to calculate AGV as a function of AGV expected for a child of the specified age, sex and birth height percentile with ACH, and the AGV reference value expected for the equivalent average stature child. In the base case, a PRAGV of 77.28% was assumed based on effectiveness data from Study 111-301 [135]. While AGV is age dependent, it is assumed in the model that the PRAGV is independent of age.

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Adverse reactions (occurrence)	Study 111-301 (safety population) Subjects with any AE (%), Event rate* Placebo: 98.4%, 34.8 Vosoritide: 98.3%, 126.7	BSC: No AE Vosoritide: Injection site reaction: 68.7 per PY Vomiting: 0.4 per PY Hypotension: 0.2 per PY Diarrhoea: 0.1 per PY Pain: 0.2 per PY	AE incidence rates were collected from study 111-301. Injection site reactions were predominantly Grade 1, with 5 events in two patients at Grade 2. Blood pressure decreases were transient and resolved without intervention; the reported events were identified predominantly during periods of frequent vital signs monitoring at clinical visits over a 52-week treatment period.
Complication rates, ACH	See section 8.1.2.3	See section 8.1.2.3	In LIAISE, health care resource use data were collected retrospectively from patient medical records, and patients were required to have a minimum of 5 years of medical records prior to recruitment. At enrolment, where available, data were collected up to 9 years previously. Event rates for complications were calculated as the number of events divided by the total number of historical years.
Complication rates, general population	See section 8.1.2.3	See section 8.1.2.3	Prevalence estimates were collected from literature sources. Annual probabilities in different age periods were calculated as $1 - (1 - \Delta CP)^{(1 \div \Delta T)}$ where ΔCP was the added cumulative probability during the period and ΔT is the length of the period in years.
HSUV	No height-dependent HRQoL utility values in ACH patients were identified.	See section 8.4	As described in section 8.4, patient utility was estimated in each cycle based on height achieved and complication history, with an age adjustment applied.

The CUA modelling was done with the aim to use the most robust clinical data from the vosoritide clinical trial programme to populate the CUA model, including the pivotal phase 3 RCT (111-301) as well as BioMarin's large European burden-of-illness study (LIAISE). Data on the effectiveness of vosoritide in restoring AGV were taken from the study 111-301, which was considered the best source of evidence to inform this parameter. Similarly, model inputs including, incidence of complications and healthcare resource use associated with achondroplasia was judged to be best informed by the LIAISE (BMN 111-501) Natural History study. The CUA model inputs are not directly informed by any results of the other studies in the clinical trial programme. Rather, these results were used as supportive evidence of efficacy and durability of effect. For example, data from the 111-205 study with up to 7.5 years of follow-up show that the vosoritide treatment effect is durable, and this supports the assumption of durability in the CUA model.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The Danish patient population: As described above (section 4.4), the approved indication of vosoritide in EU is for the treatment of ACH in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of ACH should be confirmed by appropriate genetic testing [1]. This corresponds to the patient population expected to be treated with vosoritide in Denmark. Based on the indication, there are currently approximately 30-32 patients in Denmark in the age span of 2-15 years, whereof about 75% is likely to be considered for vosoritide treatment [19, 20].

Patient population in the clinical documentation submitted: The clinical documentation describes placebo-controlled, randomised RCTs (study 111-206 + extension study 111-208 and 111-301 + extension study 111-302), dose escalation studies (111-202 + extension study 111-205), as well as non-interventional natural history studies conducted in patients aged 0–18 years and adults (111-901, 111-501). The study population for vosoritide included subjects aged 2–18 years with ACH, documented by clinical grounds and confirmed by genetic testing and thus the study data are representative for the targeted patient group. The applicability of the study population to the Danish patient population was also confirmed by communication with clinical experts in Denmark [19, 20].

Patient population in the health economic analysis submitted: In the base case, the modelled population reflects the EMA licensed indication: patients with ACH aged 2 years and older, confirmed by genetic testing, with open growth plates [1]. For the modelling, the age of growth plate closure is assumed to occur at 15 years for the average patient. Clinical experts indicate that on average, epiphyseal closure occurs between 14-16 years old in females and 15-17 years old in males, which is also supported by literature [39]. As the model requires an average stopping age across genders, 15 years old was taken as an average.

Scenario analyses were performed where various ranges of treatment starting and stopping age were assessed.

Table 20. Patient population

Patient population Important baseline characteristics	Clinical documentation/indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age range	2-18 years [25, 29, 31, 33, 115]	Treatment starting age: 2 years Treatment stopping age: 15 years	Patients between 2 years and epiphyseal closure based on input from clinical experts [19, 20]

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2): The intervention is vosoritide, administered subcutaneously daily at a dose of 15 µg/kg. Pre-filled syringes are available in three sizes (400 µg, 560 µg, and 1.2 mg) [1]. It is expected that the Danish clinical practice will follow the recommendations stated in the SmPC [1]. This corresponds to the treatment protocol applied in the clinical trial program (Table 21).

Intervention in the clinical documentation submitted: The dose in study 301/302 was administered in accordance with the recommendations stated in the SmPC [1].

Intervention as in the health economic analysis submitted: The model assumes that all children cease treatment on reaching 15 years of age. In addition, the model assumes that 0.86% of children will discontinue treatment each year, based on treatment adherence observed in Study 111-301 over 1 year [153]. The estimate is also supported by long-term data from Study 111-302 where only 8 out of 119 patients discontinued after approximately 3 years of treatment [111]. The low discontinuation rate reflects the low frequency of serious adverse events in the trial, and the strong perceived need for treatment. On the assumption that discontinuation of treatment due to administration burden or side effects is unlikely to occur years after treatment initiation, the extrapolation of the rate observed over the first year to subsequent years is conservative.

Table 21. Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Single daily dose; volume according to dosing schedule (Table 7).	Single daily dose; one syringe per day consumed.	Single daily dose; volume according to dosing schedule (Table 7). One syringe per day will be consumed.
Length of treatment (time on treatment) (mean/median)	Daily treatment	CEM output: mean time on treatment 12.3 years (Table 45)	Daily treatment, continuously until treatment discontinuation criteria is met.
Criteria for discontinuation	Treatment with this medicinal product should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses [1]. Annual discontinuation rate in study 111-301 was 0.86%.	Annual probability of discontinuation is 0.86%, until 15 years of age when treatment is assumed to stop for all patients. Applying the same stopping age for all patients is a simplification, representing average time point of epiphyseal closure.	Treatment with this medicinal product should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses [1]
The pharmaceutical's position in Danish clinical practice	First line treatment	First line treatment	First line treatment

8.2.2.3 Comparators

Vosoritide is an innovative treatment with no equivalent existing comparator. There are currently no licensed treatments available addressing the underlying cause of ACH. Therefore, best supportive care, which focuses on mitigating complications associated with untreated ACH [2], is considered to be the only and thus most relevant comparator for the economic evaluation.

The current Danish clinical practice (as described in 5): Current standard of care is focused on managing the range of symptoms and complications that each patient presents with.

Comparators(s) in the clinical documentation submitted: Placebo/Standard of care/

Comparators in the health economic analysis submitted: For the cost-effectiveness modelling, the outcomes of best supportive care are informed by the natural history studies in the clinical study program for vosoritide [33].

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: The pivotal Phase III study 111-301 assessed the effect of daily vosoritide administration on annualized growth velocity (AGV), growth (height Z-score), and body proportions (upper to lower body segment ratio) in subjects treated with vosoritide compared with the placebo group, as well as further characterization of its safety and tolerability in children with ACH. The study also evaluated the QoL and daily function of subjects through health-related QoL (HRQoL) and functional independence assessments.

Relevance of the documentation for Danish clinical practice: Annualized growth velocity is a well-established height measure allowing for follow-up on growth rate during childhood and adolescence. It is a key indicator of skeletal growth; well-documented over the paediatric age range; highly sensitive to factors that impact growth negatively or positively; and easily and objectively measurable in an accurate non-invasive manner[1].

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The relative efficacy outcomes in the submitted health economic analysis: In the model, growth is simulated based on normalised age specific AGV data. The impact of vosoritide treatment is modelled as percentage recovery of AGV (PRAGV), representing the increase in AGV compared with the ACH natural history, applied for each year the patient receives treatment. Data on the effectiveness of vosoritide in restoring AGV were taken from the pivotal Phase 3 study, Study 111-301. In addition to the treatment effect on growth, the increase in bone growth attributable to vosoritide is also assumed to reduce the likelihood of complications arising from ACH.

Table 22. Summary of text regarding value

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study: **Annualized growth velocity (AGV)**	Difference between the vosoritide group and the placebo group in the mean change from baseline in AGV at the 52-week time point: **1.7 (1.22, 1.93), P<0.0001**	The treatment effect is modelled as percentage recovery of expected AGV (PRAGV). The PRAGV is used to calculate AGV as a function of AGV expected for a child of the specified age, sex and birth height percentile with ACH, and the AGV reference value expected for the equivalent average stature child. In the base case, **a PRAGV of 77.28%** was estimated based on effectiveness data from Study 111-301. To estimate the PRAGV, the percentage recovery of AGV_{as} was first calculated for vosoritide and placebo in age groups 5-7 years, 8-10 years, and 11-14 years; then a weighted mean of percentage recovery of AGV_{as} was calculated for each arm. The PRAGV was then calculated as the ratio of the difference between the percentage recovery of AGVas in the vosoritide and placebo arms, and 1 minus the percentage recovery of AGVas in the placebo arm. The weighted mean of the percentage AGVas in the vosoritide and placebo arms was 66.8% and 92.4%, respectively. This generated the PRAGV of 77.28%.

Table 23. Summary of text regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Annualized growth velocity (AGV)	AGV was derived from the height measurements of subjects. This parameter required two height assessments for each subject and is annualized to cm/year. AGV as well as other growth parameters evaluated in these studies reflect experience from previous studies of approved growth products. [154, 155]	It is a key indicator of skeletal growth; well-documented over the paediatric age range; highly sensitive to factors that impact growth negatively or positively; and easily and objectively measurable in an accurate non-invasive manner[1]	Growth rate (AGV) based on height measurement is a standard measurement for patients with ACH and is followed during growth.

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: Safety data collected in the placebo-controlled phase III trial 111-301 included observed rates per treatment arm and incidence (%) of AE of any grade, SAEs, treatment related AE, AE of CTCAE grade ≥ 3, death, and EOI. The proportion of subjects experiencing AEs and SAEs that led to study drug interruption was similar between the vosoritide (10 [16.7%] and 2 [3.3%] subjects, respectively) and placebo (10 [16.4%] and 2 [3.3%] subjects, respectively) groups [126].

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Adverse reaction outcomes in the health economic analysis submitted: AE incidence rates were collected from study 111-301. Injection site reactions were predominantly Grade 1, with 5 events in two patients at Grade 2. Blood pressure decreases were transient and resolved without intervention; the reported events were identified predominantly during periods of frequent vital signs monitoring at clinical visits over a 52-week treatment period.

Table 24. Adverse reaction outcomes

Adverse reaction outcome	Clinical documentation[1]	Used in the model (numerical value)
Injection site reaction	68.7 per PY	68.7 per PY
Vomiting	0.4 per PY	0.4 per PY
Hypotension	0.2 per PY	0.2 per PY
Diarrhoea	0.1 per PY	0.1 per PY
Pain	0.2 per PY	0.2 per PY

Source: [1]Study 111-301 CSR [109]

8.3 Extrapolation of relative efficacy

Not applicable.

8.3.1 Time to event data – summarized:

Not applicable.

8.4 Documentation of health-related quality of life (HRQoL)

In the model, patient outcomes are quantified as quality-adjusted life years (QALYs). For each year in the model, a health state utility value (HSUV) is calculated as a function of patient age, height, and comorbidities. The number of years the simulated patient lives is summed after weighting each year with the HSUV and discounting, to calculate lifetime QALYs. The difference between the lifetime QALY total with and without treatment with vosoritide is the incremental gain in QALYs estimated for that simulated patient with vosoritide.

8.4.1 Overview of health state utility values (HSUV)

A literature review searching for HRQoL and health state utility value (HSUV) in ACH [156] did not retrieve any utility data that were useful for the model. The majority of the literature did not report data suitable for the generation of HSUVs. A few studies did report data collected with the EQ-5D. However, the studies did not provide sufficient data to estimate the improvement in QoL associated with an increase in height.

Instead, the approach described hereunder was used to estimate the HSUV in the model. The HSUV for the simulated patient is initially estimated based on the patients' z-score using a regression model being estimated from data in the Health Survey for England (HSE) [40]. An age adjustment multiplier is applied based on the patient's age at the given cycle, based on Danish population values [157]. A multiplier is then applied to the HSUV for each existing comorbidity with values estimated from the literature. After application of all relevant multipliers, an additive disutility is added to the HSUV for relevant complications in the year in which they occur, while a utility increment is assumed for patients that reach heights above a disability threshold of 150 cm. Effects on caregiver HRQoL were not included in the base case, but explored in a scenario analysis.

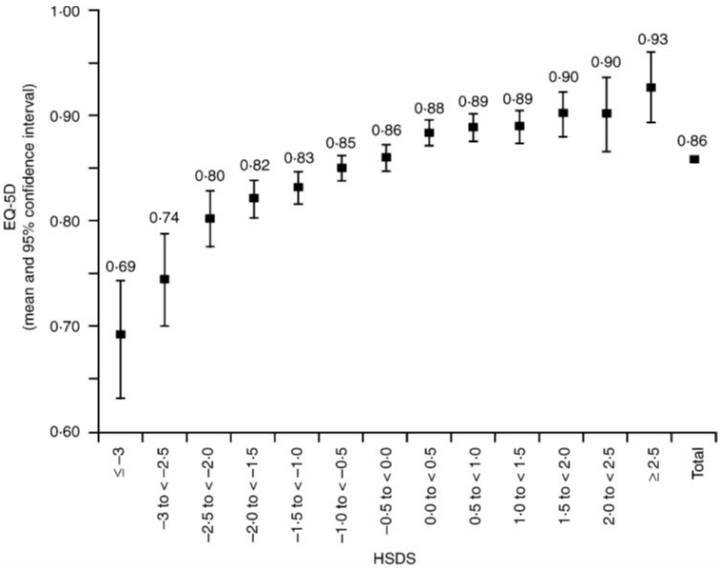
The available HRQoL data were not possible to map to Danish EQ-5D.

8.4.2 Health state utility values used in the health economic model

8.4.2.1 Adjustment of HSUV as a function of height

In order to estimate a multiplier for the disutility arising from short stature, data from HSE were used. Christensen and colleagues analysed height and EQ-5D-3L data on 14,416 HSE respondents [40]. The raw data are presented in Figure 40.

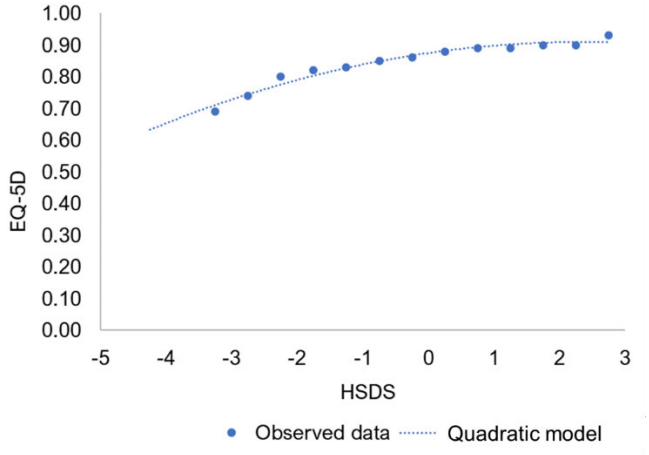
Figure 40. Relationship between height standard deviation score and EQ-5D score (mean & 95% CI) from Christensen 2007



Abbreviations: HSDS, height standard deviation score.
Source: Christensen, 2007 [40]

The data on EQ-5D score and height standard deviation score (HSDS) from Christensen and colleagues were modelled. The HSDS is the z-score for height – the number of standard deviations different from the mean value. The mean HSDS score for each bin in Figure 40 was assumed to be the middle of the range, and values at the extremes (HSDS ≥ 2.5 and HSDS ≤ -3) were excluded. A quadratic model generated a good fit (R=0.96) to the observed data (Figure 41). Addition of a cubic term generated little meaningful improvement in fit and unrealistic extrapolated values.

Figure 41. Comparison of modelled and observed EQ-5D score as a function of HSDS



To facilitate combination of the impact of height, age and other comorbidities on QoL, the model thus applied a quadratic polynomial relationship between HSDS and QoL. In the base case a regression model was fitted to the published HSUVs for respondents with heights below 2 HSDS under the mean value. The resulting quadratic polynomial function was:

$$\text{Utility} = -0.0064 \times HSDS^2 + 0.0298 \times HSDS + 0.8748$$

Table 25 reports predicted EQ-5D values for HSDS from -7.0 to -2.0 for the quadratic model. This range is considered most representative of patients with ACH who are unlikely to reach a height of 2 HSDS below the mean. Table 25 also reports values used in a scenario analysis, derived using a linear regression model fitted to the published HSUVs for respondents with heights below 2 HSDS under the mean value.

Table 25. Predicted EQ-5D score from the quadratic model and simplified linear model as a function of HSDS

HSDS	EQ-5D prediction – quadratic model (Base case)	EQ-5D prediction – linear model (Scenario)
-2	0.79	0.85
-2.5	0.76	0.81
-3	0.73	0.77
-3.5	0.69	0.73
-4	0.65	0.69
-4.5	0.61	0.65
-5	0.57	0.62
-5.5	0.52	0.58
-6	0.47	0.54
-6.5	0.41	0.50
-7	0.35	0.46

Abbreviations: HSDS, heigh standard deviation score.

The approach to adjustment of HSUV for height assumes a causative relationship between short stature and QoL as observed in the HSE data. It further assumes that the impact of height on QoL is independent of age and sex. This approach to adjusting HSUVs for changes in height has previously been applied in the National Institute for Health and Care Excellence (NICE) technology appraisal for somatropin for the treatment of growth failure in children (TA188) [158].

8.4.2.2 Age adjustment of HSUV by patient age

In the model, age-dependent HSUV multipliers are estimated based on quality-of-life data measured with EuroQol 5-Dimension (EQ-5D) in the Danish general population (Table 26) as guided by the DMC [157]. The study did not report utility values for the age span 0-17 years. For this age span, it was assumed in the current model that the HSUV was the same as in the adjacent age span.

The multiplier at a given age represents the percentage decrement comparing the HSUV at that age relative to the general population HSUV at baseline.

Table 26. Health state utility values by age, from the Danish general population

Age span	HSUV[1]	Age adjustment multiplier[2]
0-17	0.871	1.00
18-29	0.871	1.00
30-39	0.848	0.97

Age span	HSUV[1]	Age adjustment multiplier[2]
40-49	0.834	0.96
50-59	0.818	0.94
60-69	0.818	0.94
70-79	0.813	0.93
80-88	0.721	0.83
89+	0.721	0.83

[1] Source: Medicinrådet, 2021 [157]

[2] Calculated as HSUV by age ÷ HSUV at baseline (0.871).

8.4.2.3 Adjustment of HSUVs for comorbidities – multipliers

Data on HSUVs associated with comorbidities were obtained from the literature.

Table 27 reports the multiplier for each complication along with the literature source and the duration over which the multiplier is applied. No multiplier was applied for DCS or shunt surgery. No suitable value could be found for leg bowing and tympanostomy. The multiplier for leg-bowing was assumed to be equal to that for kyphosis/lordosis. The multiplier for tympanostomy was assumed the same as that for chronic pain, on the assumption that recurrent bouts of otitis media preceding tympanostomy are associated with chronic pain.

The assumptions on duration were mainly based on the outcome of the global advisory board [152], and were further validated by Danish clinical experts [131], who agreed on all estimates but two: those for kyphosis/lordosis and for leg bowing, which were reduced from lifetime to 2 years' duration. The global Delphi panel estimates for these complications were assessed in a scenario analysis.

The combined impact of all relevant complications at a given cycle was used to generate a decremental complication disutility by multiplying the product of all factors with the age-dependent HSUV for the general population. The difference between the resulting value and the age-dependent HSUV represented the decremental utility associated with complications at the given cycle:

[Utility decrement] = [General population HSUV by age] – [General population HSUV by age] × [Multiplier, complication 1] × [- - -] × [Multiplier, complication n].

Table 27. HSUV multipliers representing the disutility associated with comorbidities

Complication	Multiplier	Duration[1]	Source, multiplier
Sleep apnoea	0.920	Lifetime	Schmidlin 2010 [159]
Spinal stenosis	0.790	Lifetime	Nayak 2019 [160]
Kyphosis/lordosis	0.916	10 years	Abodor 2010 [161]
Leg bowing	0.916	10 years	Assumption
CVD	0.798	Lifetime	Pockett 2018 [162]
Depression	0.798	Lifetime	Wu 2015 [163]
Chronic pain	0.725	Lifetime	Wu 2015 [163]
Hearing loss	0.896	Lifetime	Baek 2016 [164]
Orthodontic surgery	0.940	1 year	Sullivan 2011 [165]
Tympanostomy	0.725	1 year	Assumption
Obesity	0.950	Lifetime	Sach 2007 [166]

Abbreviations: CVD, cardiovascular disease; HSUV, health state utility value.

[1] Source: The assumptions on duration were mainly based on the outcome of a global advisory board [152]..

8.4.2.3.1 HSUV multiplier for obstructive sleep apnoea

Studies reporting the disutility associated with obstructive sleep apnoea were limited. The study by Schmidlin and coworkers estimated HSUVs in 66 patients with obstructive sleep apnoea using EQ-5D-3L and direct elicitation techniques [159]. Data collected using the EQ-5D-3L was valued using UK tariffs to generate a HSUV of 0.92, which was used directly in the model.

8.4.2.3.2 HSUV multiplier for spinal stenosis

The HSUV for spinal stenosis was derived from a recent systematic review of QoL for patients undergoing spinal surgery [160]. The study reported pooled EQ-5D scores before and after different types of spinal surgery. The pooled post-operative EQ-5D score for lumbar stenosis was 0.640, and the mean age of patients was 71. The Danish general population utility is 0.81 at age 71 (Table 26). Hence the multiplier for spinal stenosis (post-surgery) was calculated as 0.64/0.81=0.790.

8.4.2.3.3 HSUV multiplier for kyphosis/lordosis

Data on QoL for patients with kyphosis/lordosis were limited. Data on QoL have been reported for patients with scoliosis [161]. The study reports EQ-5D data valued using UK tariffs for 57 Norwegian patients with scoliosis of which 39% had undergone surgery and 30% were scheduled for surgery. The median age was 21 years and 84% were female. The mean EQ-5D score was 0.83. The general population utility at the age of 21 in Norway is 0.906 [167]. Hence the multiplier for kyphosis/lordosis was calculated as 0.83/0.906=0.916.

8.4.2.3.4 HSUV multiplier for leg bowing

No suitable data were located to estimate a HSUV associated with leg bowing. Consequently, the multiplier for leg bowing was assumed to be the same as the multiplier for kyphosis/lordosis.

8.4.2.3.5 HSUV multiplier for CVD

The literature on QoL with CVD is extensive. A recent large UK study was utilised to estimate a value for the model[162]. The study followed 2,103 patients for two years and reported QoL measured using EQ-5D-3L at 6-month intervals for different cardiac conditions. Over half of patients (56%) had experienced an MI. The data indicated little change over 2 years compared with data at 12 months following MI. The HSUV peaked at 12 months (0.708) compared with 0.89 for the general population, generating a multiplier of 0.708/0.89=0.798.

8.4.2.3.6 HSUV multiplier for depression

A number of studies have published data on QoL in depression. A recent systematic review reported HSUVs of 0.56, 0.45 and 0.25 for mild, moderate and severe depression, respectively [168]. A pooled analysis of trial data reported similar values of 0.57, 0.52 and 0.39 for mild, moderate, and severe depression, respectively [169]. The HSUV multiplier for depression was derived from a large, recent analysis of UK data [163]. The study utilised EQ-5D data and data on comorbidities from 13,955 participants from South Yorkshire, UK. Multivariate regression analysis was used to estimate a disutility of 0.172 associated with depression. The study reported a population norm for EQ-5D of 0.853. The multiplier was calculated as (0.853–0.172)/0.853=0.798.

8.4.2.3.7 HSUV multiplier for chronic pain

The HSUV for chronic pain was derived from the study used to estimate the multiplier for depression [163]. Multivariate regression generated a disutility of 0.235 associated with pain. In tandem with the reported population norm of 0.853, the two values were used to calculate a multiplier of (0.853–0.235)/0.853=0.725.

8.4.2.3.8 HSUV multiplier for hearing loss

Data on QoL with hearing loss measured using EQ-5D is limited, reflecting a perceived lack of sensitivity of the instrument to defects in hearing. A large, recent study estimated the impact of hearing impairment on QoL using EQ-5D data collected as part of the Korean National Health and Nutrition Examination Survey NHANES [164]. Regression

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analysis of data on 16,449 respondents estimated a tariff value of 0.86 for participants with moderate or severe hearing impairment compared to 0.96 for those without impairment. The multiplier was calculated as 0.86/0.96=0.896.

8.4.2.3.9 HSUV multiplier for orthodontic treatment

Limited data were available on QoL for patients undergoing orthodontic treatment. The HSUV used in the model was derived from the recent review of EQ-5D scores for chronic conditions [170]. The review reports a HSUV of 0.78 for a dentofacial anomaly based on UK tariff data. The source of the original HSUV was the catalogue of EQ-5D scores for the UK published by Sullivan and coworkers [165]. The corresponding value for the general population is reported as 0.83. Hence the multiplier for orthodontic treatment was calculated as 0.780/0.830=0.940.

8.4.2.3.10 HSUV multiplier for obesity

In scenario analysis a reduction in QoL was assumed for patients with a BMI exceeded 30. Data on the impact of obesity were taken from a UK population study which analysed the relationship between BMI and EQ-5D-3L responses for 1,865 patients aged 45 or older [166]. A disutility of -0.04 was estimated through regression analysis. This was used to derive a HSUV multiplier 0.95 alongside the mean EQ-5D-3L value of 0.803 reported for patients of normal weight (BMI 18 to 25) in the study.

8.4.2.3.11 HSUV multiplier for tympanostomy

No suitable data were located to estimate a HSUV associated with tympanostomy. Consequently, tympanostomy was assumed to be associated with a reduction in HRQoL equivalent to chronic pain for 1 year only.

8.4.2.4 Adjustment of HSUVs for comorbidities – disutilities associated with events

A disutility is added to patients' HSUV for the year in which surgery is undertaken for certain complications (Table 28). This disutility captures the impact of undergoing the surgical procedure and the degeneration in QoL in the immediate period prior to the procedure. Disutilities are applied for the year in which patients undergo surgery for spinal stenosis, kyphosis/lordosis, leg bowing, DCS, and shunt insertion, or experience a CVD event. No adjustment is included for orthodontics or tympanostomy. In both cases the multiplier applied over a single year was assumed to capture any disutility associated with treatment procedures.

Table 28. Disutilities associated with surgery and CVD events

Complication	Disutility	Source
Spinal stenosis	-0.263	Nayak 2019 [160]
Kyphosis/lordosis	-0.263	Assumed same as spinal stenosis
Leg bowing	-0.263	Assumed same as spinal stenosis
CVD event	-0.150	Matza 2015 [171]
DCS	-0.244	Nayak 2019 [160]
Shunt insertion	-0.070	Matza 2014 [172]
Limb lengthening	-0.521	Hafez 2022 [173]

Abbreviations: CVD, cardiovascular disease; DCS, decompression surgery.

8.4.2.4.1 Disutility for musculoskeletal surgery

The disutility for spinal stenosis was derived from the systematic review which informed the multiplier for spinal stenosis [160]. The review reported pre-operative and post-operative pooled EQ-5D scores of 0.377 and 0.640 for lumbar stenosis, respectively. The difference between the pre-operative and post-operative score (0.263) was calculated as the additional disutility for the year in which patients undergo surgery for spinal stenosis.

No suitable source could be found to estimate the disutility associated with surgery for kyphosis/lordosis or leg bowing, and consequently the disutility of surgery was assumed the same as for spinal stenosis.

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8.4.2.4.2 Disutility for CVD event

Inevitably, most of the literature on QoL in patients with CVD reports QoL after a CVD event. Data on the disutility attributable to the event are scarce. In response to the lack of data on the acute impact of CVD events, Matza and co-workers undertook a valuation exercise to estimate HSUVs for three cardiovascular events during the acute phase and for the years following the event [171]. The three events valued were stroke, acute coronary syndrome, and heart failure. Valuations were obtained from the UK general population using a time trade-off (TTO) exercise to value health state vignettes. The vignettes for the acute phases encompassed the experience of the event, and the course of recovery over one year. The vignettes for the chronic phases reflected ongoing symptoms in the years following the event. The mean TTO values for stroke, acute coronary syndrome and heart failure in the acute phase were 0.33, 0.67 and 0.60, respectively. The mean TTO values for stroke, acute coronary syndrome and heart failure in the chronic phase were 0.52, 0.82 and 0.57, respectively. The disutility of a CVD event was calculated as the difference in acute and chronic TTO values for acute coronary syndrome (–0.15).

8.4.2.4.3 Disutility for DCS

Data on cervical radiculopathy were included in the systematic review of QoL in patients undergoing spine surgery [160]. The pooled pre-operative and post-operative EQ-5D scores were 0.500 and 0.744, respectively, generating a disutility of –0.244.

8.4.2.4.4 Disutility for shunt insertion

No data were found on QoL for infants undergoing shunt insertion. Data reporting QoL before and after shunt surgery in adults for idiopathic normal pressure hydrocephalus were considered inappropriate as the clinical manifestations of the condition are more limiting than hydrocephalus in infants [174]. The disutility attributable to shunt surgery was taken from a study estimating HSUVs for skeletal complications in patients with bone metastases. The events included surgery to stabilize a bone and HSUV were estimated by direct elicitation from the UK general population using TTO. A disutility of –0.07 was estimated for surgery.

8.4.2.4.5 Disutility for limb lengthening

A recent study has published data on QoL in children undergoing distraction osteogenesis [173]. The study reported HSUVs generated from the EQ-5D-Y and the Child Health Utility 9D (CHU-9D) instruments. The study compared utility values at 1 month, 3 months and 9 months after initiating treatment in 16 children receiving lower limb correction using magnetic nails and 18 children receiving lower limb correction using the standard Ilizarov technique (external fixation). The latter technique was considered most relevant for children undergoing limb lengthening. Mean EQ-5D-Y scores at 1, 3 and 9 months were 0.08, 0.3 and 0.54. It was assumed that QoL at baseline following surgery was the same as at 1 month, and that children recovered to full health (score of 1.0) at 12 months. Linear interpolation between measurements generated 0.479 QALYs over one year. On an assumption that children would otherwise experience full health the disutility associated with limb lengthening was calculated as -0.521.

8.4.2.5 Utility increment from exceeding height threshold

In the Nordic advisory board [175], the clinical experts stated that over certain height thresholds, the QoL improves substantially. This improvement would be due to achieving an ability to reach and move around independently and without aids and support when crossing this threshold, i.e., avoiding the disability associated with the short stature. Along this discussion, it was the experts' opinion that the regression model based on Christensen data more probably underestimates than overestimates the potential QoL gain from height improvement, and that a larger quality-of-life gain was expected when height improves from 145 to 155 cm as compared with 155 to 165 cm [175].

To account for this clinical opinion in the CE model, an incremental utility was applied in cycles where the patient height exceeds a height threshold. In the base case, a height threshold of 150 cm was applied, based on the above mentioned clinical expert statement that pinpointed the raise from 145 to 155 cm as important [175], and an incremental utility of 0.10 was arbitrarily assumed. Alternative input values were assessed in sensitivity analyses.

8.4.2.6 Disutility associated with adverse events

The AE profile associated with vosoritide is generally mild. Instances of pain, diarrhoea and vomiting are occasionally experienced, and carers administering treatment require training to mitigate the risk of hypotension. However, the only common AE recorded is an injection site reaction. The AEs associated with treatment with vosoritide were considered mild and transient, and hence no disutility associated with AEs was included in the model.

8.5 Resource use and costs

The CE analysis provided in this HTA submission is performed with a Danish perspective.

The model includes four broad cost components: pharmaceutical costs, health care resource use, one-off costs of interventions for complications, and ongoing costs for management of complications. Costs were estimated from Danish sources in Danish krona (DKK), where possible. Healthcare unit costs were sourced from Danish Diagnosis related groups (DRG) costs from 2023 [176], research publications, specialist takstkort at laeger.dk and Kommunernes og Regionernes Løndatakontor. Pharmaceutical prices were derived from medicinpriser.dk.

8.5.1 Cost A: Pharmaceutical costs, vosoritide treatment

8.5.1.1 Resource use for cost A

Vosoritide is administered once daily by SC injection at a dose of approximately 15 µg/kg, with recommended dosing as presented in Table 7[1]. The drug is supplied in a prefilled syringe at three doses: 400 µg, 560 µg, and 1.2 mg. The recommended daily dose never exceeds one vial, and since vial sharing is not expected in clinical practice, the drug consumption will be one syringe per day (either 0.4 mg, 0.56 mg, or 1.2 mg solvent).

Data from Study 111-301 indicates a mean participant weight of 23.8 kg and a maximum of 68.9 kg [30]. No vial sharing was assumed in the base case. Based on data from Study 111-301, it was assumed that patients would miss an average of 4.4 doses per year, generating an estimate of 360.85 doses per year.

8.5.1.2 Unit cost for cost A

All vial sizes are provided at the same cost of **DKK 35,250 per 10-vial pack**, which generates a fixed daily drug cost irrespective of patient weight.

8.5.1.3 Value used in the model for cost A

The annual cost of vosoritide applied in the model was DKK 1,271,996, as outlined in Table 29.

Table 29. Annual cost of vosoritide

Pharmaceutical	Cost per pack (AIP DKK)	Units per pack	Cost per unit (AIP DKK)	Annual consumption	Annual cost (AIP DKK)	Source
Vosoritide	35,250.00	10	3,525.00	360.85	1,271,996	BioMarin

8.5.2 Cost B: Pharmaceutical costs, comparator

8.5.2.1 Resource use for cost B

There is currently no approved drug treatment for ACH in Denmark. Consequently, no cost was assumed for any comparator drug treatment.

8.5.2.2 Unit cost for cost B

N/A

8.5.2.3 Value used in the model for cost B

N/A

8.5.3 Cost C: Hospital costs, administration training vosoritide

8.5.3.1 Resource use for cost C

Administration of vosoritide is done subcutaneously, at home, by the caregiver. However, when the treatment is initialised, a hospital visit would be required where a healthcare professional should train caregivers on the preparation and subcutaneous injection of this medicinal product; train caregivers and patients to recognise signs and symptoms of decreased blood pressure; and inform caregivers and patients what to do in the event of symptomatic decreases in blood pressure [1].

8.5.3.2 Unit cost for cost C

The DRG cost used for administration training of vosoritide is **DKK 2,150** for 2023 (DRG 08MA99 [176]).

8.5.3.3 Value used in the model for cost C

The cost for administration training of vosoritide (Table 30) is applied once in the model, at the initiation of treatment (first cycle).

Table 30. Cost of administration training

Cost item	Number of units	DKK per unit	Source
Cost of administration training	1	2,150	DRG 08MA99 [176]

8.5.4 Cost D: Pharmaceutical cost, medication related to ACH

8.5.4.1 Resource use for cost D

Patients were assumed to receive multidisciplinary care and support regardless of whether they are treated with vosoritide or not. This includes routine drug treatment with antibiotics, analgesics, and anti-inflammatories. Data on medication use related to ACH were collected in LIAISE [10] and indicated an event rate of medication use of 7.3, 8.6 and 4.7 per 100 person years was reported for systemic antibacterials, analgesics and anti-inflammatories, respectively.

The same resource use per cycle was assumed in both treatment arms, hence differences in total medication costs only relates to differences in life length between the treatment arms.

8.5.4.2 Unit cost for cost D

Drug unit costs were collected from medicinpriser.dk [177] and AIP prices were applied in the model as specified in Table 31.

8.5.4.3 Value used in the model for cost D

Table 31 reports the estimate of the annual costs of medications for the three most common types of medication reported in LIAISE [10]. The annual cost is calculated from the pack cost (Table 31) obtained from the medinpriser.dk drug pricing web portal [177]. These data generated an estimated annual cost of **DKK 1.01** per patient for medications related to ACH.

Table 31. Annual costs of medication estimated for drug use related to ACH management

Pharmaceutical	Cost / pack (AIP DKK)	Units / pack	Cost / unit	Dose per day	Usage per 100 PY	Annual cost	Source
Antibacterials for systemic use [1]	100	30	3.33	3	7.3	0.73	Medicinpriser.dk [177]
Analgesics [2]	11.32	100	0.11	8	8.6	0.08	Medicinpriser.dk [177]
Anti-inflammatories [3]	65.11	30	2.17	2	4.7	0.20	Medicinpriser.dk [177]

[1] Amoxicillin "Nordic Prime". [2] Paracetamol "Zentiva". [3] Naproxen "Nordic Prime". Abbrevations: PY, person years.

8.5.5 Cost E: Hospital costs, complications

8.5.5.1 Resource use for cost E

The costs of complications are split into costs associated with the immediate management of the complication applied in the year of occurrence of the event, and costs of ongoing medical care management. The following complications were assumed to require ongoing medical care to manage: obstructive sleep apnoea, CVD, depression, chronic pain, obesity, and hearing loss. The cost of ongoing medical care was applied in the model once in each year after incidence including the incident year. Costs for sleep apnoea were assumed to be zero following a successful surgical intervention.

8.5.5.2 Unit cost for cost E

Hospital resources were costed using DRG costs for 2023 [176] and the literature [178-180] as presented in detail in Table 32.

For obesity, myocardial infarction (MI) and depression, DRG based costs were not considered relevant based on lack of a specific surgical procedure associated with the complication. In these cases, the complication costs were estimated based on literature sources. The cost for depression was estimated based on a Danish register-based study by Christensen et al 2022 [178], in which the authors described case annual healthcare costs for somatic services (EUR 2,157), psychiatric services (EUR 3,188), primary health care (EUR 528) and subsidized prescriptions (EUR 580). The cost of a cardiovascular event was estimated based on a European report regarding cardiovascular disease statistics [179]. The Danish health care costs associated with CVD and the prevalence in men and women were reported and utilized to calculate the model cost inputs. The cost of obesity was estimated based on a Danish cost-of-illness study by Spanggaard et al 2022 [180].

8.5.5.3 Value used in the model for cost E

The costs per event specified in Table 32 were applied in the model upon incidence of an event for the immediate management costs, and once per year from the incidence and onwards for subsequent ongoing management costs, for applicable complications.

Table 32. Complication costs, immediate and ongoing management

Complications and surgeries	Immediate management cost, DKK	Subsequent ongoing management cost, DKK	Source
Decompression surgery	51,826	N/A	DRG 08MP06 [176]
Shunt insertion	129,783	N/A	DRG 26MP19 [176]
Limb lengthening	74,722	N/A	DRG 08MP38 [176]
Chronic pain	5,630	5,630	DRG 23SP01 [176]
Depression	53,311	53,311	Christensen et al. 2022 [178][1]
Hearing loss/deafness	37,427	4,271	Immediate: DRG 03MP24 [176] Ongoing: 03PR04 [176]
Laminectomy (spinal stenosis)	93,664	N/A	DRG 01MP02 [176]
Myocardial infarction (cardiovascular event)	16,712	16,712	Wilkins et al 2017 [179][2]
Obesity	25,475	25,475	Spanggaard et al 2022 [180][3]
Orthodontic surgery	55,380	N/A	DRG 03MP11 [176]
Osteotomy (leg bowing)	20,259	N/A	DRG 08MP66 [176]
Sleep apnoea	45,581	3,374	Immediate: DRG 04MP05 [176] Ongoing: 04MA02 [176]
Spinal fusion (kyphosis)	225,661	N/A	DRG 08MP01 [176]
Tympanostomy	37,427	N/A	DRG 03MP24 [176]

[1] Average annual health care costs of depression in Denmark, 2017 (EUR 6,453) × Annual exchange rate 2017 (7.439 DKK/EUR) × CPI adjustment factor (average 06.2022 – 05.2023 ÷ 2017; 1.1106). [178, 181, 182]

[2] Total health care costs of CVD in Denmark, 2015 (EUR 961,596,000) ÷ Prevalence of CVD in Denmark, 2015 (486,913 patients) × Annual exchange rate 2015 (7.459 DKK/EUR) × CPI adjustment factor (average 06.2022 – 05.2023 ÷ 2015; 1.1346). [179, 181, 182]

[3] Average direct healthcare costs per year, 2020 (EUR 3,146) × Annual exchange rate 2020 (7.454 DKK/EUR) × CPI adjustment factor (average 06.2022 – 05.2023 ÷ 2020; 1.0846). [180-182]

8.5.6 Cost F: Health care costs associated with ACH disease management

8.5.6.1 Resource use for cost F

Estimates on annual visit rates for medical contacts related to ACH were collected by Danish clinical expert input [183]. Table 33 reports contact rates with different types of health care professional by age subgroup. These rates were applied in the CE model.

The same resource use per cycle was assumed in both treatment arms, hence differences in ACH disease management costs only relates to differences in life length between the treatment arms.

Table 33. Annual number of visits to different types of medical professionals, by age group, for patients with ACH in Denmark

Type of professional	Event rate per patient and year, by age subgroup				
	0-4 y N=100; PHY=431.0	5-10 y N=121; PHY=494.9	11-15 y N=79; PHY=291.8	16-40 y N=125; PHY=704.3	>40 y N=42; PHY=239.5
Cardiologist	0.5	0	0	0	0.1
Dietician	1	1	1	0.55	0.05
ENT physician	1.5	0.75	0.6	0.05	0.05
Emergency doctor	0	0	0	0	0
General practitioner	1	0	0	0	0
Geneticist	3	1.5	0.5	0.5	0.5
Neurologist	0	0	0	0	0.5
Neurosurgeon	1.1	0.55	0.05	0.05	0.1
Occupational therapist	1	0	0	0	0
Ophthalmologist	1	0.5	0	0	0
Orthopaedic surgeon	1.25	0.75	0.75	0.55	0.225
Other surgeon, other professional	0	0	0.5	0.5	0
Paediatrician	2	1.5	1	1	0.5
Physiotherapist	1.1	0.5	0	0.05	0.55
Respiratory physician	1.25	0	0	0.05	0.05
Speech therapist	0.6	0	0	0	0
Other consultant	0.5	0	0	0	0

8.5.6.2 Unit cost for cost F

Healthcare professional costs were sourced from the agreement between Praktiserende Lægers Organisation (PLO), Foreningen af Speciallæger (FAS) and the Regions [184, 185] by April 2023 except for dietician, occupational therapist and physiotherapist where gross income per month was sourced from Kommunernes og Regionernes Løndatakontor [186] and calculated as per the DMC's Værdisætning af enhedsomkostninger to a cost per hour [187].

Table 34. Unit costs per contact with healthcare professional

Healthcare professionals	Cost per contact, DKK	Description and source
Cardiologist	697.77	Takstkort 17a, 1. Konsultation, kardiologi [185]
Dietician	339.84	Ernæringsassistenter. Kommunernes og Regionernes Løndatakontor [186]
ENT physician	253.41	Takstkort 11a, 1. Konsultation, Øre-, næse- og halsspecialet [185]
Emergency doctor	769.81	Assumed same as: takstkort 19a, 1. Konsultation, paediatri [185]
General practitioner	155.24	Honorartabel 2023 (April) [184]
Geneticist	769.81	Assumed same as: takstkort 19a, 1. Konsultation, paediatri [185]
Neurologist	810.63	Takstkort 20c, 1. Konsultation, neurologi [185]
Neurosurgeon	810.63	Assumed same as neurologist
Occupational therapist	411.93	Ergoterapeuter, Kommunernes og Regionernes Løndatakontor [186]
Ophthalmologist	270.78	Takstkort 14b, 1. Konsultation, oejenlaegehjaelp [185]
Orthopaedic surgeon	703.46	Takstkort 25, 1. Konsultation, ortopædisk kirurgi [185]
Other surgeon, other professional	487.51	Takstkort 22, 1. Konsultation, kirurgi [185]
Paediatrician	769.81	Takstkort 19a, 1. Konsultation, paediatri [185]
Physiotherapist	416.57	Fysioterapeuter, Kommunernes og Regionernes Løndatakontor [186]
Respiratory physician	697.77	Takstkort 17a, 1. Konsultation, lungemedicin [185]
Speech therapist	769.81	Assumed same as: takstkort 19a, 1. Konsultation, paediatri [185]

8.5.6.3 Value used in the model for cost F

The unit costs of health care professionals (Table 34) were combined with event rates reported in Table 33 to estimate annual health care costs for medical contacts related to ACH, by age subgroups (Table 35).

Table 35. Annual health care costs for medical contacts related to ACH, by age subgroups

Age subgroup	0-4 y	5-10 y	11-15 y	16-40 y	>40 y
Annual health care cost, DKK	8,090	3,235	2,151	1,774	1,471

8.5.7 Cost G: Adverse events

8.5.7.1 Resource use for cost G

Table 36 reports the rate of AEs associated with vosoritide per person year and per person day. Injection site reactions were predominantly Grade 1, with 5 events in two patients at Grade 2. Blood pressure decreases were transient and resolved without intervention; the reported events were identified predominantly during periods of frequent vital signs monitoring at clinical visits over a 52-week treatment period.

All AEs were assumed to be managed by the carer. No costs were assumed for vomiting and hypotension. Injection site reactions were assumed to be managed with paracetamol and an antihistamine. Diarrhoea was assumed to be managed with an antidiarrheal. Pain was assumed to be managed with paracetamol.

Table 36. Yearly event rates for adverse events

Adverse event	Event rate per year[1]	Treatment assumed
Injection site erythema	68.7	Analgesic + antihistamine
Vomiting	0.4	No medication

Adverse event	Event rate per year[1]	Treatment assumed
Hypotension	0.2	No medication
Diarrhoea	0.1	Antidiarrhoeal
Headache	0.4	Analgesic

Sources: [1]Study 111-301 CSR [109].

8.5.7.2 Unit cost for cost G

Unit costs relevant for management of adverse events are presented in Table 37.

8.5.7.3 Value used in the model for cost G

The rate of each AE per year was multiplied by the daily cost of the required medications to generate an annual cost of managing each AE, assuming that each event was associated with one day of treatment. The total annual cost for AEs associated with vosoritide was **DKK 152.82** (Table 37).

Table 37. Unit costs per adverse events

Adverse event	Daily cost of medication (DKK)	Yearly cost, DKK [4]
Injection site erythema	Paracetamol: 0.91 [1] Cetirizine: 1.30 [2]	151.35
Vomiting	-	0
Hypotension	-	0
Diarrhoea	Loperamide: 8.06 [3]	0.81
Headache	Paracetamol: 0.91 [1]	0.36
Total		**152.82**

Sources: [1]Table 31. [2]Daily dose 1 × 10 mg; Pack size 100 x 10 mg; Price at din Apoteker 2023-06-27: "Cetirizin Teva" DKK 129.75 [188]. [3]Daily dose 4 × 2 mg; Pack size 100 x 2 mg; lowest AIP per strength and pack size 2023-06-27: "Imodium" DKK 201.62 [177]. [4]Event rate per year × Daily cost of medication.

8.5.8 Cost H: Municipality costs

8.5.8.1 Resource use for cost H

Municipality costs were based on house and car adaptations. These were categorized as follows: children pre-school (0 to 5 years), school-going children (5 to 18 years) and adults (>18 years). The estimated percentages of patients per age group incurring adaptation costs in a given year are presented in Table 38.

In the micro-simulation model, it is determined using a random-number approach in each cycle if adaptation costs are incurred, where the probability is based on the estimates in Table 38. For vosoritide treated patients, the probability of incurring adaptation costs in each cycle was reduced in proportion to the degree of height restored in that cycle relative to the average stature height for the corresponding age and gender.

Table 38. Percent of patients requiring adaptations

Age group	Value	Source
0<5 years	0%	Estimate
5<18 years	10%	Estimate
≥ 18 years	20%	Estimate

8.5.8.2 Unit cost for cost H

The estimated annual cost of adaptation unit costs per age group are presented in Table 39.

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Table 39. Unit costs for adaptations assumed in the model

Age group	Value (DKK)	Source
0<5 years	50,000	Estimate
5<18 years	75,000	Estimate
≥ 18 years	100,000	Estimate

8.5.8.3 Value used in the model for cost H

In the micro-simulation model, the costs for adaptations (Table 39) are either applied or not applied in each cycle, based on a random number approach and the probabilities presented in Table 38. The resulting average costs of adaptations per cycle are presented in Table 40. However, these resulting averages are not directly applied in the model.

Table 40. Average costs for adaptations in the CE model

Age group	Value (DKK)	Source
0<5 years	0	Calculated
5<18 years	7,500	Calculated
≥ 18 years	20,000	Calculated

8.5.9 Cost I: Patient costs

8.5.9.1 Resource use for cost I

The patient costs considered to be of relevance for the CE model were transportation costs associated with hospital visits due to ACH management. It was estimated that ACH patients visit the hospital on average 10 times in a year.

For vosoritide treated patients, the number of hospital visits were assumed to decrease in proportion to the degree of height restored in that cycle relative to the average stature height for the corresponding age and gender. The number of visits were rounded up to the nearest integer number.

8.5.9.2 Unit cost for cost I

Transportation cost is calculated using the average distance to the hospital, 20 km as per DMC's document "Værdisætning af enhedsomkostninger" [187]. The cost per kilometer (3.73 DKK/km) is sourced from DMC's document "Værdisætning af enhedsomkostninger" [187].

8.5.9.3 Value used in the model for cost I

The patient costs for transportation associated with a hospital visit applied in the model are presented in Table 41.

Table 41. Patient costs used in the model

Cost item	Value	Source
Transportation cost per hospital visit	DKK 149.20	DMC's Værdisætning af enhedsomkostninger [187] (2 ways × 20 km × DKK 3.73/km)

8.6 Results

8.6.1 Base case overview

Table 42. Base case overview

Parameter	Description
Comparator	BSC
Type of model	Cost-utility analysis; Individual simulation model
Time horizon	Lifetime
Treatment line	First-line treatment

Parameter	Description
Measurement and valuation of health effects	LY and QALY
Included costs	• Drug costs, • Admininstration costs, • Hospital costs (management of complications), • Other health care costs (general ACH management and medication) • AE costs, • Municipality costs (aids), • Patient transport costs

8.6.2 Base case results: Vosoritide versus Best Supportive Care

Table 43 shows the deterministic results of the base case analysis with annual discounting applied (3.5% year 1-35; 2.5% year 36-70; 1.5% year 71 onwards). The results of the CE base case analysis comparing vosoritide with BSC over a lifetime horizon (Table 43) indicated that treatment with vosoritide is expected to generate 9.46 incremental QALYs (16.48 vs. 7.02) as compared with BSC. The additional total cost with vosoritide treatment was [redacted] per patient [redacted] which generated an ICER of [redacted] per QALY gained with vosoritide as compared with BSC over a lifetime horizon.

Undiscounted results showed that patients treated with vosoritide as compared with BSC are expected to gain 1.3 life years (LY) (73.8 vs. 72.5) and 28.7 additional QALYs (41.2 vs. 12.6) at an added cost of [redacted] per patient [redacted] corresponding to an undiscounted ICER of [redacted] per QALY gained. The lower ICER resulting from the undiscounted analysis implies that the health gains are sustained over longer time periods, while the added treatment costs are incurred in the front-end of the time horizon.

Table 43. Base case results, discounted analysis.

Per patient	Vosoritide	BSC	Difference
Life years gained			
Total life years gained	73.81	72.50	1.31
QALYs			
Total QALYs	16.48	7.02	9.46
QALYs; z-score	18.35	10.53	7.82
QALYs; complications	-2.75	-3.51	0.75
QALYs; achieving height threshold	0.89	0.00	0.89
Costs			
Total costs	[redacted]	[redacted]	[redacted]
Drug costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Hospital costs (complications)	[redacted]	[redacted]	[redacted]
General ACH management costs incl. medication	[redacted]	[redacted]	[redacted]
Adverse reactions costs	[redacted]	[redacted]	[redacted]
Patient time and transport costs	[redacted]	[redacted]	[redacted]
Municipality costs; aids	[redacted]	[redacted]	[redacted]

Per patient	Vosoritide	BSC	Difference
Incremental results	Intervention vs. Comparator		
ICER (per QALY)	[redacted]		

For treatments such as vosoritide, with front-end drug acquisition costs but clinical benefits that provide sustained QoL improvements over the patient's entire life span, the common application of an annual discount of costs as well as effects in the cost-effectiveness analysis makes it inherently difficult for these treatments to reach the pre-defined cost-effectiveness thresholds. In a sense, this can be seen as a down-prioritisation of patients with lifelong chronic conditions, since the QoL loss that will be experienced by untreated patients in later stages of the life due to the natural course of disease, will be associated with a lower treatment value compared with a similar QoL experienced at the current timepoint. But in the case of ACH and vosoritide, in order to provide QoL benefits in adult ages, the treatment has to be provided during the growth period, meaning that the current discounting approach will never acknowledge the full clinical value of the treatment.

8.6.2.1 Disaggregated costs

A breakdown of costs by category for vosoritide and BSC is presented in Table 44. The great majority of the cost differences arose from the cost of vosoritide treatment. The largest cost offsets accrued from the impact of improved growth were associated with lower costs for shunt insertions, management of depression, kyphosis/lordosis and CVD, as well as reduced costs for patient aids and transportation costs.

Table 44. Breakdown of costs by category for vosoritide and best supportive care. Discounted analysis.

Cost category	Vosoritide	BSC	Increment
Drug costs (primary treatment)	[redacted]	[redacted]	[redacted]
Drug administration (one-off cost of training)	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Decompression surgery costs	[redacted]	[redacted]	[redacted]
Hydrocephalus - Shunt insertion costs	[redacted]	[redacted]	[redacted]
Sleep apnoea costs	[redacted]	[redacted]	[redacted]
Spinal stenosis costs	[redacted]	[redacted]	[redacted]
Kyphosis/Lordosis costs	[redacted]	[redacted]	[redacted]
Leg bowing costs	[redacted]	[redacted]	[redacted]
Cardiovascular disease costs	[redacted]	[redacted]	[redacted]
Depression costs	[redacted]	[redacted]	[redacted]
Chronic pain costs	[redacted]	[redacted]	[redacted]
Otitis media costs	[redacted]	[redacted]	[redacted]
Hearing loss/Deafness costs	[redacted]	[redacted]	[redacted]
Dental malocclusion - orthodontic treatment costs	[redacted]	[redacted]	[redacted]
General health care management costs	[redacted]	[redacted]	[redacted]

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Cost category	Vosoritide	BSC	Increment
Medication costs	[redacted]	[redacted]	[redacted]
Municipality costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care.

8.6.2.2 Disaggregated outcomes

A comparison of outcomes by category for vosoritide and BSC is presented in Table 45. Treatment with vosoritide was associated with a mean gain in height of 22.6 cm and resulted in a gain in life expectancy of 4.2 years. The mean time on vosoritide treatment was 12.3 years. Treatment had the largest impact on the incidence of kyphosis/lordosis, hearing loss, and chronic pain leading to absolute reductions in incidence of 17.3%, 13.7% and 9.4%, respectively.

Table 45: Breakdown of outcomes by category for vosoritide and best supportive care

Outcomes	Vosoritide	BSC	Increment
Final height (cm) (97.5%, 2.5%)	150.9 (167.2, 135.3)	128.4 (140.4, 117)	22.6
Time on vosoritide (undiscounted, years)	12.3	0.0	12.3
Life years (undiscounted)	73.8	72.5	1.3
QALYs (discounted)	16.5	7.0	9.5
Incidence of complications			
Foramen magnum stenosis	12.0%	16.5%	-4.5%
Hydrocephalus	3.9%	6.3%	-2.4%
Sleep apnoea	41.7%	44.7%	-3.0%
Spinal stenosis	14.8%	21.3%	-6.5%
Kyphosis/Lordosis	40.8%	60.8%	-20.0%
Leg bowing	18.5%	26.3%	-7.8%
Cardiovascular disease	40.8%	48.3%	-7.5%
Depression	15.9%	22.0%	-6.1%
Chronic pain	32.4%	43.8%	-11.4%
Otitis media	12.7%	17.0%	-4.3%
Hearing loss/Deafness	38.3%	53.3%	-15.0%
Dental malocclusion	32.5%	35.0%	-2.5%

Abbreviations: BSC, best supportive care.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Individual parameter uncertainty was tested using univariate sensitivity analysis where all parameters were systematically and independently varied over their plausible range, determined by either the 95% CI or ± 10% where no

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estimates of uncertainty were available. Results for the ten most influential parameters are presented in Table 46 and Figure 42.

The most influential parameters were the vosoritide drug cost, the AGV improvement rate with vosoritide treatment and the coefficients in the quadratic model for HSUV by z-score. Beyond these, only minor changes in the ICER were observed in these one-way sensitivity analyses (OWSA), indicating that the results of the CE analyses were robust and that the major drivers of the CE results are the treatment cost, the treatment efficacy, and the utility modelling. The impact of changing the efficacy rate is not surprising and it should be noted that the range resulting from ± 10% is broad (69.6% - 85.0% restoration of average stature AGV).

Figure 42. Tornado diagram for the ten most influential parameters in one-way sensitivity analysis.

Abbreviations: QALY, quality-adjusted life year.

Table 46. Variation in ICER for the ten most influential parameters in one-way sensitivity analysis.

Parameter	Variation	LB input	UB input	ICER at LB	ICER at UB	Difference
Drug cost per 10-vial pack	±10%	31,725	38,775	1,179,686	1,452,638	272,951
Bone growth velocity - all ages (% normal)	±10%	0.696	0.850	1,458,215	1,205,343	252,872
Utility coefficient - quadratic	±10%	-0.006	-0.007	1,394,805	1,245,914	148,892
Utility coefficient - linear	±10%	0.027	0.033	1,349,841	1,284,122	65,719
Utility weight: Hearing Impairment	±10%	0.806	0.986	1,303,298	1,329,283	25,985
Utility benefit from exceeding disabilitating height	±10%	0.090	0.110	1,328,629	1,303,927	24,703
Utility weight: Myocardial infarction	±10%	0.718	0.878	1,309,343	1,323,052	13,709
Utility weight: Sleep apnoea	±10%	0.828	1.000	1,309,799	1,321,745	11,946
Utility weight: Pain	±10%	0.653	0.798	1,310,905	1,321,461	10,556
Utility weight: Surgery - Kyphosis	±10%	0.824	1.000	1,311,258	1,320,691	9,433

Abbreviations: ICER, incremental cost-effectiveness ratio; LB, lower bound; UB, upper bound; QALY, quality-adjusted life year.

8.7.2 Scenario analysis

Table 47 reports the results of the scenario analysis. The 15 scenarios generating the largest change from the base-case ICER are presented graphically in Figure 43. The largest increase in ICER was observed in the scenario applying discounting rates for costs and outcomes of 5%. The largest decrease in ICER resulted from applying lower discounting rates on costs and outcomes. The top four scenarios which had the largest impact on the ICER varied the discount rate

and excluded drug wastage. The sensitivity of the results to changes in the discount rate is unsurprising, given the long duration over which costs and outcomes are simulated. Using ACH growth charts from WHO rather than regional was also associated with a higher ICER.

Extensive scenario analysis examining the impact of alternative starting and stopping ages for treatment and consideration of cohorts of varying ages entering the model generated a modest range of ICERs. The lowest ICER was obtained in the scenario in which patients enter the model at ages from 2 to 5 years and treatment ceased at 14 years. The highest ICER was obtained when patients entered the model at ages from 6 to 11 years and treatment ceased at 15 years. In general, delaying treatment to 5 years of age led to modest increases in the ICER, and simulation of a mixture of ages entering the model led to increases in the ICER.

Other scenarios, such as the application of alternative estimates of the rate of complications using data from the literature in place of data from LIAISE, the exclusion of achondroplasia general management costs, and the inclusion of 10% probability of undergoing limb lengthening surgery had minimal impact on the ICER.

Table 47. Results of scenario analysis

Scenario	Incremental Costs	Incremental QALYs	ICER (QALYs)	Difference to base case
Base Case	[redacted]	[redacted]	[redacted]	[redacted]
Patient aged 2 to 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Patient aged 6 to 11 years	[redacted]	[redacted]	[redacted]	[redacted]
Patient aged 2 to 15 years	[redacted]	[redacted]	[redacted]	[redacted]
Discount rates 0%	[redacted]	[redacted]	[redacted]	[redacted]
Discount rates 5%	[redacted]	[redacted]	[redacted]	[redacted]
Discount rates 1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Use WHO growth charts	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping at 16 years	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation (5%)	[redacted]	[redacted]	[redacted]	[redacted]
Missed doses (n=36)	[redacted]	[redacted]	[redacted]	[redacted]
Exclude drug wastage	[redacted]	[redacted]	[redacted]	[redacted]
Exclude complications	[redacted]	[redacted]	[redacted]	[redacted]
Limb lengthening - 10% probability	[redacted]	[redacted]	[redacted]	[redacted]
Include caregiver utility	[redacted]	[redacted]	[redacted]	[redacted]
Exclude achondroplasia general management costs	[redacted]	[redacted]	[redacted]	[redacted]

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Scenario	Incremental Costs	Incremental QALYs	ICER (QALYs)	Difference to base case
Alternative source for complication rates	[redacted]	[redacted]	[redacted]	[redacted]
Include BMI component	[redacted]	[redacted]	[redacted]	[redacted]
Start treatment at 5, stop treatment at 14	[redacted]	[redacted]	[redacted]	[redacted]
Start treatment at 5, stop treatment at 15	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 2 to 5 years, stop treatment at 14	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 6 to 11 years, stop treatment at 14	[redacted]	[redacted]	[redacted]	[redacted]
PRAGV of 90%	[redacted]	[redacted]	[redacted]	[redacted]
PRAGV of 60%	[redacted]	[redacted]	[redacted]	[redacted]
Use linear regression model for utility	[redacted]	[redacted]	[redacted]	[redacted]
Exclude utility increment at height threshold	[redacted]	[redacted]	[redacted]	[redacted]
Lower threshold for utility increment (140 cm)	[redacted]	[redacted]	[redacted]	[redacted]
Lower utility increment at height threshold (0.05)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACH, achondroplasia; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Figure 43. Tornado plot of ICERs for 15 scenarios with greatest variation from base case

Abbreviations: ACH, achondroplasiaondroplasia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

8.7.3 Probabilistic sensitivity analyses

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters were assigned distributions and varied jointly. 500 Monte Carlo simulations were recorded, each of which included simulation of a cohort of 1,000 patients treated with vosoritide and with BSC. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

The CEP and CEAC are presented in Figure 44 and Figure 45, respectively. The CEP demonstrates virtually no uncertainty in incremental costs reflecting the fact that the known cost of drug treatment with vosoritide constituted over 98% of costs in the vosoritide arm. Overall QALY gains ranged between 8.79 and 10.16 across simulations.

Figure 44. Cost-effectiveness plane for vosoritide vs best supportive care

Abbreviations: CEP, cost effectiveness plane; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 45. Cost-effectiveness acceptability curve for vosoritide vs best supportive care

Abbreviations: ACH, achondroplasiaondroplasia; CEAC, cost effectiveness acceptability curve.

9. Budget impact analysis

9.1 Number of patients

According to the approved therapeutic indication, patients with ACH are eligible for treatment from 2 years of age until epiphyseal closure. For the purpose of the BIM, all patients at ages up to 15 were considered as potentially eligible for treatment (based on clinical feedback that epiphyseal closure typically occurs by age 14-16 years old in girls and 15-17 years old in boys).

Based on the average birth prevalence of ACH estimated to be 3.72/100,000 live births [7] and the average live birth rate in Denmark over the past years (56-63,000 live births per year [84]), the incidence in Denmark is approximately 2-3 new ACH cases each year, and the calculated number of patients in ages 2-15 would be [redacted] Danish clinical experts from the two Danish ACH reference centers validated a birth prevalence of 3 cases per year in Denmark, and reported that the current patient number in the ages 2-15 was around [redacted] [19, 20].

The clinical experts further estimated that the majority of patients (about 90%) between the ages of 2-10 years old were eventually likely to be treated; 75% of patients in ages 11-14 where the process of getting used to having the diagnosis will to some extent affect the willingness to start the treatment for some of the patients; while patients above 15 are not expected to start treatment as many patients will have either passed the epiphyseal closure, or if they are still growing, be less willing to start treatment as they will only have a short amount of time to experience treatment benefits.

The number of patients expected to be treated over the next five years was estimated using the eligible patient population by age group in Denmark, the clinicians' expectations for treatment rates and the uptake rates observed in other European markets. The budget impact model takes into account additional patients coming on to therapy and older patients dropping off treatment as they reach epiphyseal closure. Given that approximately the same number of patients will reach and leave the relevant age span each year, the total number of treatment eligible patients was assumed to be constant. The estimates of the number of treated patients over the coming years if vosoritide is introduced are reported in Table 48 [19, 20]. If vosoritide is not recommended, no patients are expected to be treated (Table 49).

Table 48. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 49. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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9.2 Expenditure per patient

Annual drug costs (vosoritide only), AE costs (vosoritide only), and health care costs were collected from the CE model. Health care costs were collected from the CE model as the resulting average undiscounted annual cost during year 1-5 for management of complications, general ACH management and medication, in the vosoritide and comparator arm respectively.

The resulting treatment costs per patient and year are presented in Table 50 and Table 51. In line with DMC guidelines the analysis assumes that all patients commence treatment at the start of each year, and a full annual treatment cost is thus applied for all patients.

Table 50. Costs per patient per year - if the pharmaceutical is recommended

		Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	Vosoritide[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSC	-	-	-	-	-
Health care costs	Vosoritide[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSC[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	Vosoritide[3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSC	-	-	-	-	-
Total costs	Vosoritide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: [1]Annual cost per patient; sourced from Table 29 in this dossier; [2]Average annual undiscounted cost during year 1-5 resulting from the CE model, per model arm; [3] Average cost per patient and year; sourced from Table 37 in this dossier.

Table 51. Costs per patient per year – if the pharmaceutical is NOT recommended

		Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	Vosoritide	-	-	-	-	-
	BSC	-	-	-	-	-
Health care costs	Vosoritide	-	-	-	-	-
	BSC[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	Vosoritide	-	-	-	-	-
	BSC	-	-	-	-	-
Total costs	Vosoritide	0	0	0	0	0
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: [1]Average annual undiscounted cost during year 1-5 resulting from the CE model, comparator arm.

9.3 Budget impact

The resulting estimated budget impact over the next five years if vosoritide is or is not introduced for the current indication is presented in Table 52 showing that the total added annual expenditure is estimated to be [redacted] in year 1, increasing to [redacted] in year 5, if vosoritide is recommended as a standard treatment. The increased cost is predominantly associated with increased treatment costs, while some savings in health care costs are expected.

Table 52. Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
If the pharmaceutical under consideration is recommended					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Health care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
If the pharmaceutical under consideration is NOT recommended					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Health care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Health care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10. Discussion on the submitted documentation

The clinical efficacy of vosoritide has been demonstrated during a clinical development program including all age groups of subjects targeted with ACH and whose epiphyses are not closed, including a randomized placebo-controlled phase III study (111-302) in subjects 5 to <18 years and its long-term extension phase (111-302) and two phase II studies and their long-term extension phase in patients aged 5 to 14 years (111-202/205) and 0 to 5 years (111-206/extension study 111-208), respectively. The vosoritide clinical development programme followed a methodological and responsible approach, by studying the least vulnerable populations first. Thus, the safety and tolerability profile of vosoritide was first established in children aged over 5 years providing proof-of-concept and evidence of long-term outcomes [22, 27] followed by safety and tolerability established for younger populations [119]. The development program also includes natural history studies of the disease to provide a robust and comprehensive external control for data from the vosoritide open-label, long-term extension studies to assess durability of treatment effect on growth over time. In particular, study 111-901 carried out by the laboratory and which made it possible to follow the patients included in the interventional studies in terms of their anthropometric measurements at least 6 months before their inclusion and put on treatment.

Clinical efficacy relative to comparator (standard of care) has been calculated measuring Annualized Growth Velocity (AGV) and height Z-score, which were primary and key secondary endpoints respectively in the vosoritide clinical trials. These endpoints are possible to measure in the follow up time of the clinical trials and they directly link to the underlying disease manifestation (disproportionate short stature). Improvements in these endpoints have been correlated with improvements in health-related quality of life of patients and expert opinion has confirmed that they impact on the daily living activities and social functioning of the patients.

The results of phase III study 111-301, patients aged 5 to <18 years, showed the efficacy of vosoritide at a dose of 15 µg / kg per day administered subcutaneously with a statistically significant difference at 52 weeks of variation compared to placebo of the annualized growth rate in favour of vosoritide [22, 27]. The improvement in AGV observed in 111-301 was maintained in the open-label extension study (111-302).

Study 111-206/111-208 includes three cohorts which were initiated sequentially in decreasing order of age:

- Cohort 1 – children aged ≥ 24 to < 60 months
- Cohort 2 – children aged ≥ 6 to < 24 months

- Cohort 3 – children aged 0 to < 6 months

Studying these cohorts separately reduces heterogeneity as it considers that AGV peaks in infancy and declines rapidly during childhood up to ~5 years of age, followed by a more gradual decline in children with ACH aged 5 –15 years. Only cohort 1 is relevant for this submission considering the EMA indication of vosoritide [4, 5]. In participants aged ≥ 24 to < 60 months and ≥ 60 months, treatment with vosoritide demonstrated a positive impact of therapy through a marked improvement in height-Z score and increase in AGV over time [119].

In patients aged 5 to 14 years study 111-202 demonstrated that treatment with vosoritide exhibited a positive dose-dependent response to AGV up to a dose of 15 µg / kg per day. In the extension study 111-205, improvement in AGV and height z-score were reported in all cohorts persisting up to 7,5 years.

Comparative analyzes between data from clinical and natural history studies showed the long-term effect of vosoritide, with a significant difference in height variation between patients treated and patients not treated with vosoritide over 5 years compared to baseline. [33]

To understand the potential treatment effect on final height, extrapolation of near FAH at 16 years of subjects from Phase II (111-205) was performed and suggest that a height close to [redacted] may be achievable with long-term treatment, where a height of 1.4-1.5m is seen as critical height to achieve normal functioning [22].

No adverse effects on bone maturation have been observed in these trials. This, combined with the improvements in body segment proportionality, suggests that longer periods of treatment with vosoritide commenced at an earlier age might result in sustained enhancement of skeletal growth, with clinically and functionally beneficial consequences. Due to the inherent variability of growth and the lesser magnitude of the pubertal growth spurt in children with ACH, these long-term effects will only be known once these children reach final adult height.

Studies 111-302 and 111-208 are open-label extension studies. The studies, 111-202/111-205 are an open, study with sequential assignment to 4 cohorts and their extension still ongoing. Because of the single-arm or sequential cohort study design and lack of randomization, results may be potentially biased. Subjects and treatment providers were not blinded. However, it should be noted that the collection of outcomes is consistently described in all three studies, the statistical methods used were adequate, and the presentation is transparent. Therefore, outcome-based reporting can be excluded for all three studies. Furthermore, no other aspects were identified in the study documents that indicate an increased potential for bias. Overall, the bias potential in all three studies at the level of the endpoint "annual growth rate" can be classified as low.

Several studies have assessed the impact of short stature on health-related quality of life (HRQoL). The LIAISE (111-501) natural history study found that greater height was associated with better QoL and functionality in children with ACH [9]. Moreover, an exploratory post-hoc analysis of data on height Z-score and HRQoL pooled from studies 111-901, 111-301 and 111-302 demonstrated a clear correlation between the magnitude of height deficit (Z score) and HRQoL relating to the Physical and Social domain scores [36]. Together these analyses suggest that improved height with vosoritide treatment is likely to lead to meaningful and durable improvements in patients QoL. Improved proportionality and symptom burden is also likely to result in substantial improvements to functional independence and ADL as well as simultaneously reducing the HCRU of patients [36]. However, HRQoL will need to be measured in the clinical studies using AGV as an endpoint to evaluate whether there is a significant impact on HRQoL. Meaningful effects of treatment on associated medical complications and HRQoL are likely to manifest over the long term and remains under investigation as part of vosoritide clinical development programme. Yet, the current analyses suggest that by improving endochondral ossification/ bone formation and improving height and proportionality outcomes, treatment with vosoritide is likely to reduce the incidence and severity of disease-related symptoms and comorbidities. ACH patients treated with vosoritide are also anticipated to experience a reduced need for surgical interventions and symptomatic medications in comparison to patients with ACH who do not receive treatment with vosoritide (natural history).

The studies in the vosoritide clinical programme demonstrate a satisfactory safety profile of vosoritide administered subcutaneously in patients with ACH regardless of their age. Most AE reported were mild to moderate; the most frequently reported AEs were injection site reactions, injection site erythema, injection site swelling, nasopharyngitis, vomiting, headache and pyrexia. Most of the AEs were not considered to be related to the study treatment; no SAEs

were considered to be related to treatment. Of the injection site reactions, all were non-serious, transient, and resolved spontaneously. No treatment-related hypersensitivity reactions or anaphylaxis were reported in phase II and III studies of the vosoritide development plan. No deaths have been reported during clinical trials and no patient has stopped treatment.

The economic evaluation was undertaken using an individual simulation model, which captures the impact of reduced stature on QoL and the incidence of complications related to ACH over the lifetime of the patient. An individual simulation model was judged to best capture the varying disease courses across people with ACH and the sequalae of complications. Growth restoration and risk reductions in ACH related complications was modelled upon vosiritide treatment. In the model, the treatment effect is modelled as percentage recovery of expected AGV (PRAGV). This is a function of AGV expected for a child of the specific age, sex, and birth height percentile with achondroplasia, and the AGV reference value expected for the equivalent average stature child. Basing the efficacy modelling on PRAGV rather than AGV was considered as the better choice for a number of reasons. AGV is age dependent, while PRAGV is assumed to be independent of age in the model. AGV is a relative value calculated using the height different between two visits, while PRAGV is more of an absolute value which compares the growth difference between achondroplasia population and the general population, with (treatment group) or without vosoritide (control group). It can also be used to control the baseline AGV difference in the treatment group vs. control group. Furthermore, using age-independent PRAGV makes it possible to estimate the vosoritide treatment effect using a larger country-specific sample, providing an average using all available data points. On the contrary, an estimation of AGV for each age based on the clinical trial data would be based on very small sample size for each age which in turn would be associated with a larger uncertainty. There is also a conceptual difference between the perspective that vosoritide treatment restores normal growth (relating to average stature), rather than adds growth (relating to ACH natural history), where the modelling takes the restoring normal growth perspective. As discussed in this dossier, the benefit of vosoritide treatment extends well beyond just adding body height, and one can therefore argue that it is more correct to describe the treatment benefit as a restoration of normal physical development. For example, in the CE model, the risk reduction for ACH complications is estimated based on the achieved recovery of growth relative to average stature individuals.

In conclusion, all the available data show that vosoritide has a favorable benefit / risk profile with an impact on the growth and dysmorphia of patients with ACH maintained over the long term, while having an acceptable safety profile.

11. List of experts

[redacted]

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List of tables in appendices

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List of figures in appendices

13. Appendix A Literature search for efficacy and safety of intervention and comparator(s)

13.1 Objective of the literature search

The objective of the review was to conduct a de novo clinical systematic literature review (SLR) to identify treatment outcomes, including clinical efficacy and safety of vosoritide for the treatment of ACH.

The original searches for the de novo SLR were run in September 2020; updates were subsequently performed in June 2021 (first update) and July 2022 (second update), the results of the two SLR updates have been integrated into one SLR hereafter referred to as broader SLR [92]. This broader SLR was used as a basis for the DMC literature search. The broad literature review had a broader scope than the literature search aimed for DMC (DMC literature search) and also included a search for studies of other potential therapies of ACH such as growth hormone therapy and limb lengthening surgery that could be of potential relevance on other markets. Since these treatments are not used in Danish clinical practice, any articles on other interventions than vosoritide were considered irrelevant for the purpose of the current DMC application and were therefore excluded from the DMC literature search.

This appendix describes the search strategy applied in the broader SLR, as well as the additional selection steps for the DMC literature search undertaken in the preparation of the DMC application, and the outcome of the DMC literature search.

13.2 Databases

Databases, registers and conference material that were used in the literature search are listed in Appendix Table 1 through Appendix Table 4.

Appendix Table 1. Bibliographic databases included in the literature search in the broader SLR

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid SP	1974 to June 30, 2022	01.07.2022
Medline	Ovid SP	1946 to June 30, 2022	01.07. 2022
Cochrane	Ovid SP	CENTRAL, to May 2022 CDSR, to June 29th 2022	01.07.2022
DARE*	University of York CRD platform	current issue as of September 11, 2020	11.09.2020

*Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects. *DARE was searched through the University of York CRD platform in the original SLR. It was not searched as part of either SLR update because the database was last updated in 2015.*

Appendix Table 2. Registers included in the search for the broader SLR

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	In the "Condition or disease" box of the advanced search page, search the following: 1. ACH 2. FGFR3 gene mutation	20.07.2022 to 25.07.2022

Database	Platform	Search strategy	Date of search
EU Clinical Trials Register (EU-CTR)	https://www.clinicaltrialsregister.eu/ctr-search/search/	In the search bar, search the following: 1. ACH 2. FGFR3 gene mutation Screen the records against the eligibility table	20.07.2022 to 25.07.2022
European Medicines Agency (EMA) clinical data portal	https://clinicaldata.ema.europa.eu/web/cdp/search/	In the search bar in the centre of the page (in the clinical data publication section of the website), search the following: 1. ACH 2. FGFR3 Open each record by clicking on the field in the "name" table and screen the interventions against those in the eligibility table.	20.07.2022 to 25.07.2022
Arzneimittel Infomrationssystem (AMIS)	https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html/	lick on the "research" button in the centre of the page. Navigate to the next page and search the following: 1. achondroplasie 2. ACH 3. FGFR3 Screen the records against the eligibility table.	20.07.2022 to 25.07.2022

Abbreviations: AMIS, Arzneimittel Informationssystem; EMA, European Medicines Agency; EU-CTR, European Union Clinical Trials Register; US NIH, United States National Institute of Health.

Appendix Table 3. Conference material included in the literature search for the broader SLR

Conference	Source of abstracts	Search strategy	Words/terms searched
The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International and European Meetings • ISPOR International 2022 • ISPOR International 2021 • ISPOR International 2020 • ISPOR International 2019	All years: https://www.ispor.org/heor-resources/presentations-database/search	All years: Under Conference, click on each congress in turn. Enter in the keyword search bar.	achondroplas* OR FGFR3* OR FGFR-3* OR "Fibroblast Growth Factor achondroplas* OR FGFR3* OR FGFR-3* OR "Fibroblast Growth Factor Receptor 3" OR dwarfism*

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Conference	Source of abstracts	Search strategy	Words/terms searched
• ISPOR International 2018 • ISPOR Europe 2021 • ISPOR Europe 2020 • ISPOR Europe 2019 • ISPOR Europe 2018			
Endocrine Society Conference (ENDO) • ENDO 2022 • ENDO 2021 • ENDO 2020 • ENDO 2019	2022: https://event-app4.eventpower.com/event_app/display/index/22ENDO 2021: https://academic.oup.com/jes/issue/5/Supplement_1 2020: https://academic.oup.com/jes/issue/4/Supplement_1?page=3#1062435-5832293 2019: https://academic.oup.com/jes/issue/3/Supplement_1#:~:text=ENDO%202019%20Abstracts%20%2D%20101st%20Annual,%2C%202019%20%E2%80%93%20New%20Orleans%2C%20Louisiana	2022: Click on Master Abstract Search in the bottom left >> click selection down arrow on "Abstract Title" and search each keyword >> apply selection >> for each hit, to go to the "Abstract" listing on the menu navigation bar (or use the link above) >> click on the topical category which houses the abstract >> locate the abstract and screen 2021, 2020, 2019: In the search bar in the top right select the dropdown for "This issue" and search the phrase.	achondroplas* OR FGFR3* OR FGFR-3* OR "Fibroblast Growth Factor Receptor 3" OR dwarfism*
European Society for Paediatric Endocrinology (ESPE) • ESPE 2021 • ESPE 2019 • ESPE 2018	2021: https://abstracts.eurospe.org/hrp/0094 2019/2018: https://abstracts.eurospe.org/search/search	2021: Open downloaded abstract book PDF >> use the ctrl+f function to identify each keyword in turn >> use a new highlighting colour for each keyword and only review abstracts containing the search term >> use the comment function to identify hit number of each keyword (number of highlighted words) >> screen each hit >> use website to locate posters of relevant abstracts 2019/2018: Enter the keyword textbox. Event series: ESPE Annual Meeting Volume or conference: ESPE2019/ESPE 2018 in turn Click apply. Sift the records giving >20% match	achondroplas* OR FGFR3* OR FGFR-3* OR "Fibroblast Growth Factor Receptor 3" OR dwarfism*
International Conference on Children's Bone Health (ICCBH)	2019: Abstract book, saved to server	Use the ctrl+f function to identify each term in turn. Highlight each term once in each abstract it is present in; use a new	1. ACH 2. FGFR 3. Fibroblast Growth Factor Receptor

Conference	Source of abstracts	Search strategy	Words/terms searched
• ICCBH 2019		highlighting colour for each search term; only review abstracts containing the search term; use the comment function to identify hit number of each search term (number of highlighted words)	4. dwarfism
Annual Clinical Genetics Meeting (ACGM) • ACGM 2022 • ACGM 2021 • ACGM 2020 • ACGM 2019	2022: https://www.acmgeducation.net/Users/LearningActivity/LearningActivityDetail.aspx?LearningActivityID=zoGOP75DvkyNjUy3Oqu7Ww%3d%3d 2021: https://acmg.planion.com/Web.User/AbsSearch?ACCOUNT=ACMG&CONF=AM21&ssoOverride=OFF&USERPID=PUBLIC&standalone=YES 2020: https://www.acmgmeeting.net/acmg2020/Public/Content.aspx?ID=3366&sortMenu=110000 2019: https://acmg.expoplanner.com/index.cfm?do=expomap.sessResults&search_type=abstracts&event_id=13&ID=3331	2022, 2021, 2020: In the keyword box/search bar, enter the keywords in turn. 2019: Under abstract type, select "Poster presentations only". In the keyword box, enter the keywords in turn:	2022, 2021, 2020: 1. ACH 2. FGFR 3. Fibroblast Growth Factor Receptor 4. dwarfism 2019: 1. ACH 2. FGFR3 3. Fibroblast Growth Factor Receptor 4. dwarfism

Appendix Table 4. Supplementary manual searches for the broader SLR

Source	Query	Results	Relevant results	Date of search
VHL	tw:(acondroplasia) OR tw:(ACH) Filter out MEDLINE hits	145	0	04.09.2020
LiSSa	(achondroplasie.tl) OU (achondroplasie.mc)	137	0	14.06.2021
CrescNet.org	Publications listed under "Wissenschaft" tab were searched	35		23.06.2021

Abbreviations: VHL, Virtual Health Library; LiSSa, Littérature Scientifique en Santé.

13.3 Search strategy

Articles were included in the systematic review if they met the eligibility criteria presented in Appendix Table 5. Eligibility for inclusion was defined using the Population, Intervention, Comparators, Outcome, Setting (PICOS) approach.

Appendix Table 5. Inclusion and exclusion criteria used in the literature review for the broader SLR

Domain	Inclusion criteria	Exclusion criteria
Patient population	• Paediatric patients (aged <18 years) with ACH • Patients with active or "open" growth plates • Mixed populations if results for paediatric patients with ACH were reported separately	• Adult populations (aged ≥18 years) • Healthy paediatric populations or paediatric patients with conditions other than ACH • Patients with fused or "closed" growth plates • Mixed populations if results for paediatric patients with ACH were not reported separately
Intervention	Pharmacological intervention: • CNP analogues (e.g. vosoritide [Voxzogo®] • Growth hormone therapies • FGR3 inhibitors (e.g. infigratinib [Truseltiq®]) • Surgical limb lengthening	• Non-pharmacological therapies • Preventative therapies
Comparator	Any or none	N/A
Outcomes	Efficacy outcomes, including: • Change in height • Growth velocity • Upper:lower body segment ratio, or other body proportion ratios • Height Z score • MRI imaging • FAH • Bone age • Bone mineral density • IGF-1 levels Safety outcomes, including but not limited to: • AEs • Treatment-related AEs • Serious AEs • Deaths • Discontinuation due to AEs • Discontinuation due to treatment-related AEs • Bone morphology/quality-related changes	• No relevant outcomes
Study design	• RCTs • Interventional non-RCTs, such as controlled (but not randomised) clinical trials and single arm clinical trials • Observational studies • SLRs and (N)MAs including studies considered relevant at the title/abstract review stage were hand-searched for any primary studies not identified from the database searches. They were excluded at the full text review stage unless they presented primary research.	N/A
Publication type	• Peer-reviewed journal articles • Letters **if** they reported primary research • Conference abstracts published in or since 2018	• Non-primary research publications, including narrative

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Domain	Inclusion criteria	Exclusion criteria
		reviews, editorials, guidelines, commentaries, opinion pieces • Conference abstracts from prior to 2018
Other	• Human subjects • Any language	N/A

Abbreviations: *AE, adverse event; N/A, not applicable; (N)MA, (network) meta-analysis; RCT, randomised clinical trial; SLR, systematic literature review.*

Search strings used are presented in the tables below.

Appendix Table 6. Search strategy, [MEDLINE] for the broader SLR

No.	Query	Results
#1	exp ACH/	2437
#2	(achondroplas$ or FGFR3$ or FGFR-3$ or Fibroblast Growth Factor Receptor 3).ti,ab,kf. or exp Receptor, Fibroblast Growth Factor, Type 3/	5051
#3	1 or 2	5887
#4	randomized controlled trials as topic/	156285
#5	randomized controlled trial/	571938
#6	random allocation/	106861
#7	double blind method/	172285
#8	single blind method/	32027
#9	clinical trial/	535489
#10	clinical trial, phase i.pt.	24001
#11	clinical trial, phase ii.pt.	38263
#12	clinical trial, phase iii.pt.	20730
#13	clinical trial, phase iv.pt.	2346
#14	controlled clinical trial.pt.	94925
#15	randomized controlled trial.pt.	571938
#16	multicenter study.pt.	323050
#17	clinical trial.pt.	535489
#18	exp clinical trials as topic/	375242
#19	controlled clinical trial/	94925
#20	multicenter study/	323050

No.	Query	Results
#21	(clinical adj trial$).ti,ab,kf.	452072
#22	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf.	189655
#23	placebos/	35918
#24	placebo$.ti,ab,kf.	237945
#25	(allocat$ adj2 random$).ti,ab,kf.	40904
#26	Randomi?ed adj2 trial$.ti,ab,kf.	392992
#27	rct.ti,ab,kf.	30254
#28	or/4-27	1942587
#29	exp Epidemiologic studies/	2973934
#30	exp Case Control studies/	1333659
#31	exp Cohort Studies/	2366531
#32	Case control.ti,ab,kf.	145705
#33	(Cohort adj (study or studies)).ti,ab,kf.	281582
#34	Cohort analy$.ti,ab,kf.	11277
#35	(follow up adj (study or studies)).ti,ab,kf.	55737
#36	(observational adj (study or studies)).ti,ab,kf.	143393
#37	Longitudinal$.ti,ab,kf.	318957
#38	retrospective$.ti,ab,kf.	927731
#39	Cross sectional.ti,ab,kf.	457734
#40	Cross-sectional studies/	431773
#41	exp Longitudinal Studies/	159066
#42	exp Follow-Up Studies/	686009
#43	exp Prospective Studies/	632145
#44	exp Retrospective Studies/	1039928
#45	(Prospective adj (study or studies)).ti,ab,kf.	198096
#46	(evaluation adj (study or studies)).ti,ab,kf.	6942
#47	(epidemiologic adj (study or studies)).ti,ab,kf.	28451
#48	((single arm or Single arm) adj3 (study or studies or trial$)).ti,ab,kf.	7841

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No.	Query	Results
#49	(Open-label adj (trial$ or stud$)).ti,ab,kf.	127750
#50	Non-blinded stud$.ti,ab,kf.	137
#51	(chart adj3 review).ti,ab,kf.	47404
#52	or/29-51	3747299
#53	exp animals/ not exp humans/	5023312
#54	(comment or editorial).pt.	1386227
#55	historical article/	368507
#56	or/53-55	6703362
#57	3 and (28 or 52)	950
#58	57 not 56	919
#59	Remove duplicates from 58	913
#60	limit 59 to dt=20210610-20220701	81
#61	limit 59 to ed=20210610-20220701	109
#62	60 or 61	140

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to June 30th 2022 (second SLR update)

Appendix Table 7. Search strategy, [Embase] for the broader SLR

No.	Query	Results
#1	exp ACH/	3186
#2	(achondroplas$ or FGFR3$ or FGFR-3$ or Fibroblast Growth Factor Receptor 3).ti,ab,kw. or exp fibroblast growth factor receptor 3/	9540
#3	1 or 2	10481
#4	"randomized controlled trial (topic)"/	229498
#5	randomized controlled trial/	715518
#6	clinical trial/	1037651
#7	exp "clinical trial (topic)"/	395111
#8	controlled clinical trial/	465899
#9	multicenter study/	327715
#10	exp randomization/	94395
#11	single blind procedure/	46606
#12	double blind procedure/	196346
#13	crossover procedure/	70768

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No.	Query	Results
#14	placebo/	382280
#15	phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	197847
#16	(clinical adj trial$).ti,ab,kw.	629380
#17	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kw.	264938
#18	placebo$.ti,ab,kw.	345527
#19	(allocat$ adj2 random$).ti,ab,kw.	50470
#20	Randomi?ed adj2 trial$.ti,ab,kw.	518399
#21	rct.ti,ab,kw.	49321
#22	or/4-21	2722741
#23	exp epidemiology/	4069461
#24	exp case control study/	207591
#25	exp Cohort analysis/	858452
#26	Case control.ti,ab,kw.	189652
#27	(Cohort adj (study or studies)).ti,ab,kw.	399098
#28	Cohort analy$.ti,ab,kw.	16922
#29	(follow up adj (study or studies)).ti,ab,kw.	69659
#30	(observational adj (study or studies)).ti,ab,kw.	220051
#31	Longitudinal$.ti,ab,kw.	430267
#32	retrospective$.ti,ab,kw.	1532454
#33	Cross sectional.ti,ab,kw.	594930
#34	cross-sectional study/	490452
#35	exp longitudinal study/	174461
#36	exp follow-up/	1856146
#37	exp prospective study/	775323
#38	exp retrospective study/	1265565
#39	exp observational study/	277900
#40	(Prospective adj (study or studies)).ti,ab,kw.	295992
#41	(evaluation adj (study or studies)).ti,ab,kw.	8488

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No.	Query	Results
#42	(epidemiologic adj (study or studies)).ti,ab,kw.	34150
#43	((single arm or Single arm) adj3 (study or studies or trial$)).ti,ab,kw.	16181
#44	(Open-label adj (trial$ or stud$)).ti,ab,kw.	22597
#45	Non-blinded stud$.ti,ab,kw.	206
#46	(chart adj3 review).ti,ab,kw.	99502
#47	or/23-46	7693259
#48	exp animals/ not exp humans/	4973277
#49	editorial.pt.	731134
#50	historical article/	805
#51	or/48-50	5696524
#52	3 and (22 or 47)	3328
#53	52 not 51	3224
#54	Remove duplicates from 53	3147
#55	limit 54 to dd=20210610-20220701	203
#56	limit 54 to dc=20210610-20220701	522
#57	55 or 56	522

Database: Embase 1974 to June 30th 2022 (second SLR update)

Appendix Table 8. Search strategy, [CDSR and CENTRAL] for the broader SLR

No.	Query	Results
#1	exp ACH/	16
#2	((achondroplas$ or FGFR3$ or FGFR-3$ or Fibroblast Growth Factor Receptor 3).ti,ab,kw. or exp Receptor, Fibroblast Growth Factor, Type 3/	126
#3	1 OR 2	127
#4	limit 3 to yr="2021 -Current"	16

Appendix Table 9. Search strategy, [DARE]

No.	Query	Results
#1	(MeSH DESCRIPTOR ACH EXPLODE ALL TREES)	4

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No.	Query	Results
#2	(achondroplas* or FGFR3* or FGFR-3* or Fibroblast Growth Factor Receptor 3)	7
#3	(#1 or #2) in DARE	1

13.4 Systematic selection of studies

The broader SLR identified 63 articles on 44 studies. However, for the DMC application the only intervention of relevance was vosoritide. Therefore, articles describing other interventions were excluded in a final selection step. In the final step 44 articles were excluded as they were not considered relevant for the DMC application, see Appendix figure 1.

Furthermore, one articles published and six NCT records describing three additional vosoritide clinical trials (one feeder study and two ongoing phase II studies) and one observational natural history study were added manually.

After these final steps of the selection process, a total of 25 citations describing nine studies were included in the DMC application (Appendix Table 10).

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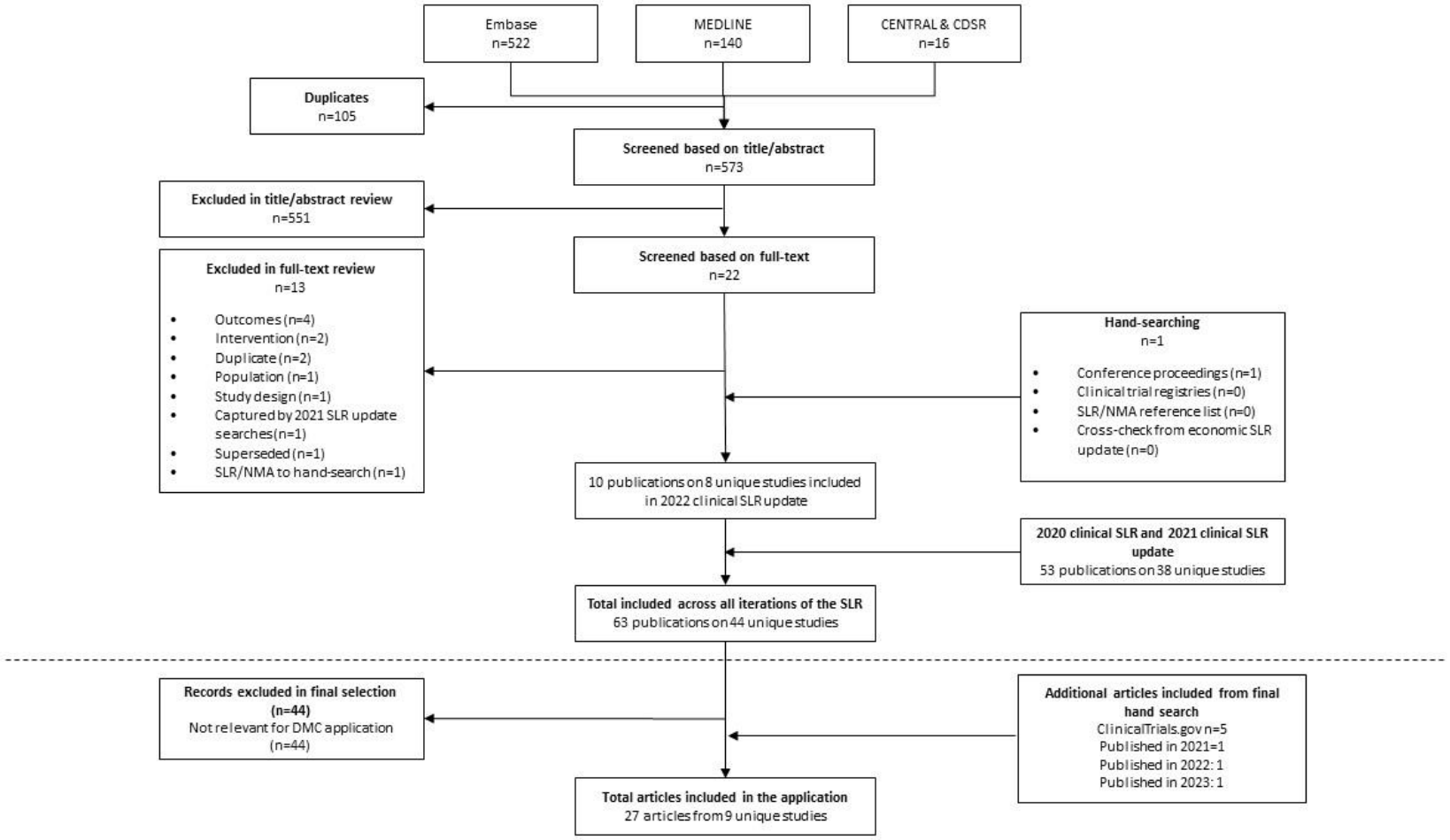
Appendix Figure 1. PRISMA flow diagram for the broader SLR and the DMC literature search



Abbreviations: *CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects*

Appendix Table 10. Studies and citations included in the DMC application

#	Study name	Reference
1-2	Study 111-301; Study 111-302	Euctr ES. A Phase 3 Study to Evaluate the Safety and Efficacy of BMN 111 in Children with ACH. *https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2015-003836-11-ES.* 2017.
		AMIS. A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN111 in Children with ACH. PharmNetBund - Clinical Trials (CT). 2017.
		JapicCTI J. A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with ACH. *https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-JapicCTI-184167.* 2018.
		NCT03197766. A Study to Evaluate the Efficacy and Safety of BMN 111 in Children With ACH. Study 111-301, Phase III, clinical study. *https://clinicaltrials.gov/show/NCT03197766.* 2017.
		Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino C, Hoover-Fong J, et al. Safe and persistent growth-promoting effects of vosoritide in children with ACH: 2-year results from an open-label, phase 3 extension study. Genetics in Medicine. 2021.
		NCT03424018. An Extension Study to Evaluate the Efficacy and Safety of BMN 111 in Children With ACH. Study 111-302, Phase III, clinical study. *https://ClinicalTrials.gov/show/NCT03424018*. 2017
		Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with ACH: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *The Lancet.* 5 - 11 September 2020;396(10252):684-692.
		Savarirayan R, Tofts L, Irving M, et al. SAT-LB18 A Randomized Controlled Trial of Vosoritide in Children With ACH. Journal of the Endocrine Society. 2020;4(Supplement_1):SAT-LB18.
		Euctr. A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with ACH. https://wwwclinicaltrialsregistereu/ctr-search/trial/2015-003836-11/results. 2020.
		Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino CA, Hoover-Fong J, et al. Persistent and Stable Growth Promoting Effects of Vosoritide in Children With ACH for up to 2 Years: Results From the Ongoing Phase 3 Extension Study. Journal of the Endocrine Society. 2021;5(Supplement_1):A670-A1
		Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino CA, Hoover-Fong J, et al. Persistent growth in children with ACH treated with vosoritide for two years: Further evidence supporting the first precision therapy for this condition. Twin Research and Human Genetics. 2021;24(5):289.

#	Study name	Reference
3-4	Study 111-202; Study 111-205	Irving M, Hoover-Fong J, Bacino C, et al. Vosoritide for children with ACH: A 30 month update from an ongoing phase 2 clinical trial. *Hormone Research in Paediatrics.* September 2018;90 (Supplement 1):76.
		NCT02055157. A Phase 2 Study of BMN 111 to Evaluate Safety, Tolerability, and Efficacy in Children With ACH. Study 111-202, Phase II, clinical study. *https://ClinicalTrials.gov/show/NCT02055157*. 2014.
		NCT02724228. A Study to Evaluate Long-Term Safety, Tolerability, & Efficacy of BMN 111 in Children With ACH (ACH) (ACH). Study 111-205, extension study. *https://clinicaltrials.gov/ct2/show/NCT02724228.* 2019.
		Savarirayan R, Irving M, Bacino CA, et al. C-Type Natriuretic Peptide Analogue Therapy in Children with ACH. *New England Journal of Medicine.* 07 04 2019;381(1):25-35.
		Euctr. A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with ACH. https://wwwclinicaltrialsregistereu/ctr-search/trial/2013-004137-32/results. 2019.
		Hoover-Fong J, Irving M, Bacino C, Charrow J, Cormier-Daire V, Polgreen L, et al. Vosoritide for children with ACH: a 60-month update from an ongoing phase 2 clinical trial. Molecular Genetics and Metabolism. 2021;132(Supplement 1):S101.
		Hoover-Fong J, Dickson, P. I.,Harmatz, P., Larimore, K., Jayaram, K., Labed, A. H., Fisheleva, E., Jeha, G., Day, J., Phillips, J. A., Savarirayan, R. Vosoritide for Children with ACH: A 60-month Update from an Ongoing Phase 2 Clinical Trial. ACGM 20212021.
5	Study 111-901;	NCT01603095. A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients With ACH. Study 111-901, Observational study. *https://clinicaltrials.gov/ct2/show/record/NCT01603095*. 2021.
		Savarirayan R, Irving M, Harmatz P, Delgado B, Wilcox WR, Philips J, Owen N, Bacino CA, Tofts L, Charrow J, Polgreen LE, Hoover-Fong J, Arundel P, Ginebreda I, Saal HM, Basel D, Font RU, Ozono K, Bober MB, Cormier-Daire V, Le Quan Sang KH, Baujat G, Alanay Y, Rutsch F, Hoernschemeyer D, Mohnike K, Mochizuki H, Tajima A, Kotani Y, Weaver DD, White KK, Army C, Larrimore K, Gregg K, Jeha G, Milligan C, Fisheleva E, Huntsman-Labed A, Day J. Growth parameters in children with achondroplasia: A 7-year, prospective, multinational, observational study. Genet Med. 2022 Dec;24(12):2444-2452. doi: 10.1016/j.gim.2022.08.015. Epub 2022 Sep 16. PMID: 36107167.
6-7	Study 111-206;	NCT03583697. A Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children With ACH. Study 111-206, Phase II Clinical Study. *https://clinicaltrials.gov/ct2/show/record/NCT03583697*. 2022.

#	Study name	Reference
	Study 111-208	NCT03989947. An Extension Study to Evaluate Safety and Efficacy of BMN 111 in Children With ACH. Study 111-208, Phase II extension study. *https://clinicaltrials.gov/ct2/show/record/NCT03989947*. 2023
		Savarirayan R, Wilcox W, Harmatz P, Phillips J, Polgreen L, Tofts L, et al. A Randomized Controlled Trial of Vosoritide in Infants and Toddlers with ACH. Endocrine Society Conference (ENDO). 2022.
8	Study 111-209	NCT04554940. A Clinical Trial to Evaluate Safety of Vosoritide in At-risk Infants With ACH. Study 111-209, Phase II clinical trial. *https://clinicaltrials.gov/ct2/show/record/NCT04554940*. 2026.
		Savarirayan R, Irving M, Maixner W, Thompson D, Offiah AC, Connolly DJ, Raghavan A, Powell J, Kronhardt M, Jeha G, Ghani S, Fisheleva E, Day JR. Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with ACH at risk of requiring cervicomedullary decompression surgery. Sci Prog. 2021 Jan-Mar;104(1):368504211003782. doi: 10.1177/00368504211003782. (31)
9	Study 111-501	NCT03449368. Lifetime Impact of ACH Study in Europe-LIAISE (LIAISE). Study 111-501, Observational study. https://clinicaltrials.gov/ct2/show/NCT03449368. 2021
		Maghnie M, Semler O, Guillen-Navarro E, Selicorni A, Heath KE, Haeusler G, Hagenäs L, Merker A, Leiva-Gea A, González VL, Raimann A, Rehberg M, Santos-Simarro F, Ertl DA, Gregersen PA, Onesimo R, Landfeldt E, Jarrett J, Quinn J, Rowell R, Pimenta J, Cohen S, Butt T, Shediac R, Mukherjee S, Mohnike K. Lifetime impact of achondroplasia study in Europe (LIAISE): findings from a multinational observational study. Orphanet J Rare Dis. 2023 Mar 15;18(1):56. doi: 10.1186/s13023-023-02652-2. PMID: 36922864; PMCID: PMC10015810.

Appendix Table 11. Overview of study design for studies included in the technology assessment/analysis

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 111-301;	Assess vosoritide administered as a	Phase III, randomised,	5 to < 18 years old, ACH, documented	Daily SC injections of vosoritide 15 µg/kg,	Change From Baseline in	Change from baseline at Week 52:

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	therapeutic option for the treatment of children with ACH.	double-blind, placebo-controlled, multi-national, multi-centre trial in patients aged 5–<18 years with documented ACH confirmed by genetic testing. Completed.	and confirmed by genetic testing	n= 60 subjects vs. Placebo, n= 61 subjects. N= 121	Annualized Growth Velocity at Week 52	• in height Z-score • in upper to lower segment body ratio • in bone metabolism biomarkers: collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP) • in QoL as measured by the Quality of Life in Short Stature Youth (QoLISSY) and Paediatric Quality of Life (PedsQL) questionnaires (every 6 months, till completion) • in functional independence as measured by WeeFIM

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						• in body proportion ratios of the extremities Incidence of Adverse Events in patients treated with vosoritide compared with control patients in the placebo group at 54 weeks
Study 111-302 (extension of 111-301)	Assess vosoritide administered as a therapeutic option for the treatment of children with ACH	Phase III, open-label, multi-centre long-term extension trial to evaluate the effect of vosoritide on growth velocity in children with ACH who completed 1 year of vosoritide or placebo treatment in the parent trial 111-301. Ongoing	Must have completed Study 111-301	Intervention: Continued vosoritide, at 15.0 µg/kg, daily subcutaneous injection (n=58) Comparator: Switched from placebo to vosoritide, at 15.0 µg/kg, daily subcutaneous injection (n=61) N= 119 enrolled from study 111-301	Change from baseline in AGV every year till completion in patients treated with vosoritide compared with patients in the placebo group	Change from baseline at week 52: • in height Z-score • in upper to lower body body segment ratio • in standing height • in body proportion ratios of the extremities • in health-related QoL as measured by the QoL in Short-Statured Youth questionnaire (every 6 months, till completion)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						• in daily activity performance as measured by Activities of Daily Living questionnaire (every 6 months, till completion) in bone metabolism biomarkers: collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP) pharmacokinetics (PK) of vosoritide (every 6 months, till completion) body proportion ratios of the extremities Incidence, severity and relationship to study drug of all treatment-emergent adverse events (TEAEs).
Study 111-202;	To evaluate the safety and tolerability of daily SC injections of	Paediatric, Phase II, non-randomized open-label dose-	5 to 14 years old at end of study ACH, documented by clinical grounds,	Vosoritide Cohort 1: daily morning dose 2.5 µg/kg (n=8)	Incidence of AEs, SAEs and clinically significant changes in vital signs,	Change from baseline at 6-months: In AGV

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	vosoritide administered to children 5–14 years of age who have a documented clinical history and a positive genetic test for ACH, administered for a total duration of 24 months divided into two phases: • an initial 6-month phase • an optional 18-month extension phase	escalation trial. Completed	confirmed by genetic testing	Cohort 2: daily morning dose 7.5 µg/kg (n=8) Cohort 3: daily morning dose 15.0 µg/kg (n=8-10) Cohort 4: daily morning dose 30.0 µg/kg (n=8-10) Comparataor NA	physical examination, ECG and echocardiogram results, imaging results, anti-vosoritide immunogenicity evaluations, and laboratory test results (urine, chemical and haematology analysis).	In height Z-score using (CDC Reference) In body proportions
Study 111-205 (Extension of 111-202)	To evaluate the long-term safety and tolerability of daily subcutaneous injections of vosoritide in children with ACH who have completed 2 years	Phase II, open-label, extension study of 111-202 dose-finding study	Have completed 24 months of BMN 111 treatment in Study 111-202.	Vosoritide Cohort 1: daily morning dose 2.5 µg/kg (n=6) Cohort 2: daily morning dose 7.5 µg/kg (n=6) Cohort 3: daily morning dose 15.0 µg/kg (n=10)	Incidence, severity, and relationship to study drug of all treatment-emergent adverse events.	Change from baseline in AGV in cm/year (interval and cumulative) Change from baseline in height Z-score Change from baseline in upper to lower body segment ratio Long-term dose exposure profile and immunogenicity of vosoritide to assess for

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	of treatment in the 111-202 study			Cohort 4: daily morning dose 30.0 µg/kg (n=8) Comparator NA		impact on safety, PK, and efficacy measures
Study 111-901	To collect baseline growth measurements on paediatric patients with ACH – Natural History Study	A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with ACH being considered for subsequent enrolment in future studies by BioMarin.		N=363		
Study 111-206;	To assess the safety and tolerability of vosoritide in patients 0 to <60 months with ACH and to assess the efficacy of vosoritide on the change in the height/length Z-score	Phase II, multicenter, randomized, double-blind, placebo-controlled study lasting 60 weeks (52 weeks of treatment). Patients were included in three age Cohorts based on their age when screening the study.	Diagnosis of ACH, confirmed by genetic testing Age 0 to < 60 months at study entry (Day 1)	Vosoritide Cohort 1: 15 µg/kg/day SC injection (all patients) Cohort 2: 30 µg/kg/day adjusted to 15 µg/kg/day when patients reach 2 years of age Vs. Placebo. N=75	Z-Score for height/length at 52 weeks.	Tolerance and tolerability: adverse event (AE), serious adverse event (SAE), clinically significant variation in vital signs, clinical examination, electrocardiogram (ECG), results of imaging and laboratory tests (urine, chemical, hematologic). AGV at week 52 Evaluation of the effect of vosoritide on bone morphology by bilateral

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						radiographs of the lower limbs, radiographs of the lumbar spine and DXA of the whole body and spine.
Study 111-208 (extension study to 111-206)	To evaluate the safety and efficacy of vosoritide in children with ACH who complete 111-206, until they reach near adult final height	Phase II, multicentre, open-label long-term extension trial.	Patients who have completed Study 111-206	Vosoritide Cohort 1: 15 µg/kg/day SC injection (all patients) Cohort 2: 30 µg/kg/day adjusted to 15 µg/kg/day when patients reach 2 years of age Comparator: NA N= 70	Adverse events (AEs), SAEs, and clinically significant changes in vital signs, physical examination, electrocardiogram (ECG), imaging, and laboratory test results (urinalysis, chemistry, haematology). Length/height Z-score at Week 52.	AGV measures Upper to lower segment body ratio and proportion ratios of the extremities Bone metabolism biomarkers: collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP) QoL, developmental status, and functional independence using age-specific questionnaires including Bayley III, WeeFIM (Functional Independence Measure), infant toddler quality of life (ITQoL), child behaviour checklist (CBCL)
Study 111-209	To evaluate Safety of vosoritide in at-	Ongoing randomized, Controlled, Open-	Age 0 to ≤ 12 months, at study entry (Day 1). Have	Vosoritide + Standard of Care (standard of care	Incidence of Treatment-Emergent Adverse	-

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	risk infants with ACH	label Clinical Trial With an Open-label Extension	ACH, documented by genetic testing.	treatment for cervicomedullary compression and once daily subcutaneous injection of vosoritide at 30µg/kg (ages 0 - <2 years old) or 15 µg/kg (ages >2 years old)) Comparator: NA N=estimated 20	Events [Safety and Tolerability] Evaluate the effect of Vosoritide on total foramen magnum volume (in cm3) by MRI volumetric measurement software	
Study 111-501	The Impact of ACH on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial State of individuals with ACH in Europe (Lifetime Impact of ACH Study in Europe (LIAISE))	Observational, retrospective, cross-sectional in patients with ACH aged 5 years and older in Sweden, Germany, Spain, Italy, Austria and Denmark. Ongoing and data cut-off 01 Nov 2019	ACH subjects of all ages at participating EU study sites	No study drug was administered. Comparator NA	Standing height, PedsQoL, QoLISSY, WeeFIM,	Other endpoints, results not included in this application: Healthcare resource use

Abbreviations: ACH: ACH; AE: Adverse events; BSAP: bone-specific alkaline phosphatase; CBCL: child behaviour checklist; CXM: collagen X biomarker; DXA: DUAL X-ray absorptiometry; ECG: electrocardiogram; ITQoL: infant toddler quality of life; MRI: Magnetic resonance imaging; PK: pharmacokinetics; QoLISSY: Quality of Life in Short Stature Youth; SAE: serious adverse event; TEAE: treatment-emergent adverse events; WeeFIM: Functional Independence Measure;

Appendix Table 12. Studies excluded after full-text review for the broader SLR and the DMC literature search

#	Reference	Reason for exclusion
1	AbouEl-Ella SS, Tawfik MA, Abo El-Fotoh WMM, Elbadawi MA. Study of congenital malformations in infants and children in Menoufia governorate, Egypt. Egyptian Journal of Medical Human Genetics. October 2018;19(4):359-365.	No relevant interventions
2	Abousamra O, Shah SA, Heydemann JA, et al. Sagittal Spinopelvic Parameters in Children With ACH. Spine Deformity. January 2019;7(1):163-170.	No relevant interventions
3	Abreu F, Protzenko T, Bellas A, Salomao JF. ACH: Neurosurgical findings. Series of cases in a reference center. Child's Nervous System. June 2019;35 (6):1069.	No paediatric patients with ACH
4	ACcomplisH China: a Phase 2, Multicenter, Randomized, Placebo-controlled, Dose Escalation Trial Evaluating Safety, Efficacy, and Pharmacokinetics of Multiple Subcutaneous Doses of TransCon CNP Administered Once Weekly in Children With ACH. 2022.	No relevant outcomes
5	Afsharpaiman S, Saburi A, Waters KA. Respiratory difficulties and breathing disorders in ACH. Paediatric Respiratory Reviews. December 2013;14(4):250-255.	Not a relevant study design
6	Ain MC, Abdullah MA, Ting BL, et al. Progression of low back and lower extremity pain in a Cohort of patients with ACH. Journal of Neurosurgery: Spine. September 2010;13(3):335-340.	No paediatric patients with ACH
7	Ain MC, Shirley ED, Pirouzmanesh A, Skolasky RL, Leet AI. Genu varum in ACH. Journal of Pediatric Orthopaedics. May/June 2006;26(3):375-379.	No relevant interventions
8	Alonso Hernandez J, Galan Olleros M, Miranda Gorozarri C, Egea Gamez RM, Martinez Caballero I, Ramirez Barragan A, et al. Two-stage bone lengthening with reuse of a single intramedullary telescopic nail in patients with ACH. Developmental Medicine and Child Neurology. 2022;64(SUPPL 3):9	Superseded
9	Apajasalo M, Sintonen H, Rautonen J, Kaitila I. Health-related quality of life of patients with genetic skeletal dysplasias. European Journal of Pediatrics. Feb 1998;157(2):114-121.	No paediatric patients with ACH
10	Arasimowicz E, Syczewska M. [A method for prediction of growth in children with ACH]. Pediatr Endocrinol Diabetes Metab. 2008;14(4):237-241.	No relevant interventions
11	Armstrong J, Pacey V, Tofts L. A retrospective cohort study of medical complications in an Australian population of children with ACH. Twin Research and Human Genetics. 2021;24(5):328-9.	No relevant intervention/comparator
12	Atanda A, Wallace M, Bober MB, Mackenzie W. Arthroscopic treatment of discoid lateral meniscus tears in children with ACH. Journal of Pediatric Orthopaedics. 2016;36(5):e55-e58.	No relevant interventions
13	Beals RK, Stanley G. Surgical correction of bowlegs in ACH. Journal of Pediatric Orthopaedics Part B. July 2005;14(4):245-249.	No paediatric patients with ACH
14	Berkowitz RG, Grundfast KM, Scott C, Saal H, Stern H, Rosenbaum K. Middle ear disease in childhood ACH. Ear Nose Throat J. May 1991;70(5):305-308.	No paediatric patients with ACH
15	Bethem D, Winter RB, Lutter L. Spinal disorders of dwarfism. Review of the literature and report of eighty cases. Journal of Bone and Joint Surgery - Series A. 1981;63(9):1412-1425.	No paediatric patients with ACH

#	Reference	Reason for exclusion
16	Bhatti NA, Mumtaz S, Malik S. Epidemiological study of congenital and hereditary anomalies in Sialkot District of Pakistan revealed a high incidence of limb and neurological disorders. Asian Biomedicine. 19 Dec 2019;13(2):49-60.	No paediatric patients with ACH
17	Bloemeke J, Sommer R, Witt S, et al. Cross-cultural selection and validation of instruments to assess patient-reported outcomes in children and adolescents with ACH. Quality of Life Research. 15 Sep 2019;28(9):2553-2563.	No relevant interventions
18	Blondel B, Launay F, Glard Y, Jacopin S, Jouve J, Bollini G. Limb lengthening and deformity correction in children using hexapodal external fixation: preliminary results for 36 cases. Orthop Traumatol Surg Res. Oct 2009;95(6):425-430.	No paediatric patients with ACH
19	Borkhuu B, Nagaraju DK, Chan G, Holmes Jr L, MacKenzie WG. Factors related to progression of thoracolumbar kyphosis in children with ACH: A retrospective Cohort study of forty-eight children treated in a comprehensive orthopaedic center. Spine. July 2009;34(16):1699-1705.	No relevant interventions
20	Brooks JT, Ramji AF, Lyapustina TA, Yost MT, Ain MC. Low prevalence of anterior and posterior cruciate ligament injuries in patients with ACH. Journal of Pediatric Orthopaedics. 01 Jan 2017;37(1):e43-e47.	No paediatric patients with ACH
21	Buratti ME, Eickhoff J, Modaff P, Pauli RM, Legare JM. Weight gain velocity in infants with ACH. American Journal of Medical Genetics, Part A. 01 Jan 2020;182(1):146-149.	No relevant interventions
22	Cao J, Kong L, Meng F, Zhang Y, Shen Y. Impact of obesity on lumbar spinal surgery outcomes. Journal of Clinical Neuroscience. 01 Jun 2016;28:1-6.	Not a relevant study design
23	Ceroni JRM, Soares DCQ, Testai LC, et al. Natural history of 39 patients with ACH. Clinics (Sao Paulo, Brazil). 02 Jul 2018;73:e324.	No relevant interventions
24	Chan ML, Qi Y, Larimore K, Cherukuri A, Seid L, Jayaram K, et al. Pharmacokinetics and ExposureResponse of Vosoritide in Children with ACH. Clinical Pharmacokinetics. 2022;61(2):263- 80.	No relevant outcomes
25	Chan ML, Qi Y, Larimore K, Cherukuri A, Seid L, Jayaram K, et al. Pharmacokinetics and ExposureResponse of Vosoritide in Children with ACH. 2021	Duplicate
26	Cheung MS, Irving M, Cocca A, et al. ACH Foramen Magnum Score: Screening infants for stenosis. Archives of Disease in Childhood 2021;106:180-184.	No relevant intervention
27	Citron K, Veneziale C, Marino J, Carter EM, Jepsen KJ, Raggio C. Bone robusticity in two distinct skeletal dysplasias diverges from established patterns. Journal of Orthopaedic Research. November 2017;35(11):2392-2396.	No relevant interventions
28	Cole TJ, Del Pino M, Adamo P, et al. Pubertal growth in height, sitting height and leg length in ACH. Annals of Human Biology 2021;48:8-14.	No relevant intervention
29	Dai WQ, Gu XF, Yu YG. [Exploring the clinical genetic characteristics and height for age growth curve of 210 patients with ACH in China]. Zhonghua Er Ke Za Zhi. Jun 02 2020;58(6):461-467.	No relevant interventions
30	Del Pino M, Fano V, Adamo P. Growth velocity and biological variables during puberty in ACH. Journal of Pediatric Endocrinology and Metabolism. 28 Mar 2018;31(4):421-428.	No relevant interventions

#	Reference	Reason for exclusion
31	de Vries OM, Johansen H, Fredwall SO. Physical fitness and activity level in Norwegian adults with ACH. American Journal of Medical Genetics. Part A 2021;185:1023-1032.	No paediatric patients with ACH
32	del Pino M, Fano V, Adamo P. Height growth velocity during infancy and childhood in ACH. American Journal of Medical Genetics, Part A. June 2019;179(6):1001-1009.	No relevant interventions
33	Del Pino M, Fano V, Adamo P. Growth in ACH, from birth to adulthood, analysed by the JPA-2 model. Journal of Pediatric Endocrinology & Metabolism 2020;33:1589-1595.	No relevant interventions
34	Dougherty H, Shaunak M, Irving M, Thompson D, Cheung MS. Identification of characteristic neurological complications in infants with ACH by routine MRI screening. Hormone Research in Paediatrics. September 2018;90 (Supplement 1):82.	No relevant interventions
35	Eralp L, Kocaoglu M, Ozkan K, Turker M. A comparison of two osteotomy techniques for tibial lengthening. Arch Orthop Trauma Surg. Jun 2004;124(5):298-300.	No paediatric patients with ACH
36	Euctr GB. A Phase 2 Study to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with ACH. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-003826-18-GB. 2018.	Not a relevant study design
37	Euctr GB. A Phase 2 study to evaluate the safety, efficacy and pharmacokinetics of TransCon CNP in prepubertal children with ACH. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2019-002754-22-GB. 2019.	Not a relevant study design
38	Euctr GB. Open-label clinical trial with an open-label extension to investigate the safety of BMN 111 in infants and young children with ACH. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2020-001055-40-GB 2020.	No relevant outcomes
39	Euctr PT. Phase 2 study of safety, tolerability, PK and efficacy of recifercept in ACH. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2020-001189-13-PT 2020.	No relevant outcomes
40	Fernandes JA, Devalia KL, Moras P, Pagdin J, Jones S, McMullan J. Screening for spinal stenosis in achondroplastic patients undergoing limb lengthening. J Pediatr Orthop B. Mar 2014;23(2):181-186.	No relevant interventions
41	Fowler ES, Glinski LP, Reiser CA, Horton VK, Pauli RM. Biophysical bases for delayed and aberrant motor development in young children with ACH. J Dev Behav Pediatr. Jun 1997;18(3):143-150.	No relevant interventions
42	Franke J, Simon M, Hein G. Ilizarov techniques of leg lengthening. Problems and results. [German]. Der Orthopade. Jun 1992;21(3):197-209.	No paediatric patients with ACH
43	Ginebreda I, Campillo-Recio D, Cardenas C, Tapiolas J, Rovira P, Isart A. Surgical technique and outcomes for bilateral humeral lengthening for ACH: 26-year experience. Musculoskelet Surg. 01 Dec 2019;103(3):257-262.	No paediatric patients with ACH

#	Reference	Reason for exclusion
44	Gollust SE, Thompson RE, Gooding HC, Biesecker BB. Living with ACH in an average-sized world: An assessment of quality of life. American Journal of Medical Genetics. 01 Aug 2003;120 A(4):447-458.	No paediatric patients with ACH
45	Gollust SE, Thompson RE, Gooding HC, Biesecker BB. Living with ACH: attitudes toward population screening and correlation with quality of life. Prenatal Diagnosis. Dec 15 2003;23(12):1003-1008.	No paediatric patients with ACH
46	Gomez Prat A, Garcia Olle L, Ginebreda Marti I, Gairi Tahull J, Vilarrubias Guillamet J. [Lumbar canal stenosis in ACH. Prevention and correction of lumbosacral lordosis]. An Esp Pediatr. Feb 2001;54(2):126-131.	No paediatric patients with ACH
47	Gooch C, Halsey MH, Blount J, Hurst A. Management of neonatal ACH: A geosocial approach in Alabama. Journal of Investigative Medicine. February 2020;68 (2):704.	No relevant interventions
48	Goyal M, Gupta A, Bhandari A, Faruq M. ACH: Clinical, Radiological and Molecular Profile from Rare Disease Centre, India. Journal of Pediatric Genetics. 2021.	No relevant intervention/comparator
49	Hammouda AI, Jauregui JJ, Gesheff MG, Standard SC, Herzenberg JE. Trochanteric Entry for Femoral Lengthening Nails in Children: Is It Safe? Journal of Pediatric Orthopaedics. 2017;37(4):258-264.	No paediatric patients with ACH
50	Hashmi SS, Gamble C, Hoover-Fong J, et al. Multicenter study of mortality in ACH. American Journal of Medical Genetics, Part A. November 2018;176(11):2359-2364.	No relevant interventions
51	Hecht JT, Francomano CA, Horton WA, Annegers JF. Mortality in ACH. American Journal of Human Genetics. 1987;41(3):454-464.	No relevant interventions
52	Helenius I, Saarinen A, White K, et al. Similar Deformity Correction, but Limited Spinal Growth and Lower Health Related Quality of Life in Children with Skeletal Dysplasia Undergoing Growth-Friendly Management for Early-Onset Scoliosis. A Matched Comparison with Idiopathic Early-Onset Scoliosis. Spine Deformity. November 2019;7 (6):1014.	No paediatric patients with ACH
53	Hiraki SI, Nakamura I, Okazaki H, Nakamura K, Kurokawa T. Skin behavior during leg lengthening in patients with ACH and hypochondroplasia: A short-term observation during leg lengthening. Journal of Orthopaedic Science. May 2006;11(3):267-271.	No paediatric patients with ACH
54	Hoernschemeyer DG, Atanda A, Dean-Davis E, Gupta SK. Discoid meniscus associated with ACH. Orthopedics. May-June 2016;39(3):e498-e503.	No relevant interventions
55	Hoover-Fong J, Bober M, Hashmi S, et al. ACH natural history: A large, ongoing multi-center Cohort study. Journal of Bone and Mineral Research. November 2018;33 (Supplement 1):121-122.	No paediatric patients with ACH
56	Hoover-Fong J, McGready J, Schulze K, Alade AY, Scott CI. A height-for-age growth reference for children with ACH: Expanded applications and comparison with original reference data. American Journal of Medical Genetics, Part A. May 2017;173(5):1226-1230.	No relevant interventions
57	Hoover-Fong JE, Schulze KJ, McGready J, Barnes H, Scott CI. Age-appropriate body mass index in children with ACH: Interpretation in relation to indexes of height. American Journal of Clinical Nutrition. 01 Aug 2008;88(2):364-371.	No relevant interventions

#	Reference	Reason for exclusion
58	Hoover-Fong JE, Alade AY, Hashmi SS, et al. ACH Natural History Study (CLARITY): a multicenter retrospective cohort study of ACH in the United States. Genetics in Medicine 2021;18:18.	No relevant outcomes
59	Horton WA, Rotter JI, Rimoin DL, Scott CI, Hall JG. Standard growth curves for ACH. Journal of Pediatrics. 1978;93(3):435-438.	No relevant interventions
60	Hosny GA. Humeral lengthening and deformity correction. J. Dec 2016;10(6):585-592.	No paediatric patients with ACH
61	Hunter AG, Bankier A, Rogers JG, Sillence D, Scott CI, Jr. Medical complications of ACH: a multicentre patient review. Journal of Medical Genetics. Sep 1998;35(9):705-712.	No relevant outcomes
62	Hwu WL, Wang TR. A clinical observation of ACH. Zhonghua Minguo xiao er ke yi xue hui za zhi [Journal]. 1991 1991;Zhonghua Minguo xiao er ke yi xue hui. 32(4):208-213.	No relevant interventions
63	Iliadis AD, Wright J, Stoddart MT, Goodier WD, Calder P. Early results from a single centre's experience with the STRYDE nail a cause for concern? Bone and Joint Journal. 2021;103 B(6):1168- 72.	Irrelevant study design
64	Ireland PJ, Donaghey S, McGill J, et al. Development in children with ACH: A prospective clinical Cohort study. Developmental Medicine and Child Neurology. June 2012;54(6):532-537.	No relevant interventions
65	Ireland PJ, Johnson S, Donaghey S, et al. Developmental milestones in infants and young australasian children with ACH. Journal of Developmental and Behavioral Pediatrics. January 2010;31(1):41-47.	No relevant interventions
66	Ireland PJ, Johnson S, Donaghey S, et al. Medical management of children with ACH: Evaluation of an Australasian Cohort aged 0-5 years. Journal of Paediatrics and Child Health. May 2012;48(5):443-449.	No relevant interventions
67	Ireland PJ, McGill J, Zankl A, et al. Functional performance in young Australian children with ACH. Developmental Medicine and Child Neurology. October 2011;53(10):944-950.	No relevant interventions
68	Ireland PJ, Ware RS, Donaghey S, et al. The effect of height, weight and head circumference on gross motor development in ACH. Journal of Paediatrics and Child Health. February 2013;49(2):E122-E127.	No relevant interventions
69	Ireland PJ, Savarirayan R, Pocovi T, et al. Development of the Screening Tool for Everyday Mobility and Symptoms (STEMS) for skeletal dysplasia. Orphanet Journal of Rare Diseases 2021;16.	No relevant interventions
70	Jprn U. Distraction osteogenesis with culture expanded bone marrow cells for patients with skeletal dysplasias and short stature. http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000007646. 2012.	No paediatric patients with ACH
71	Kaissi AA, Farr S, Ganger R, Hofstaetter JG, Klaushofer K, Grill F. Treatment of varus deformities of the lower limbs in patients with ACH and hypochondroplasia. Open Orthop J. 2013;7:33-39.	Not a relevant study design

#	Reference	Reason for exclusion
72	Khoo M, Shah MA, Saifuddin A. Natural history of the cervical high-intensity intramedullary lesion in ACH. Spinal Cord Series and Cases 2021;7:46.	No paediatric patients with ACH
73	Kim SJ, Agashe MV, Song SH, Choi HJ, Lee H, Song HR. Comparison between upper and lower limb lengthening in patients with ACH: A retrospective study. Journal of Bone and Joint Surgery - Series B. January 2012;94 B(1):128-133.	No paediatric patients with ACH
74	Kim SJ, Balce GC, Agashe MV, Song SH, Song HR. Is bilateral lower limb lengthening appropriate for ACH?: Midterm analysis of the complications and quality of life. Clinical Orthopaedics and Related Research. February 2012;470(2):616-621.	No paediatric patients with ACH
75	Kim SJ, Pierce W, Sabharwal S. The etiology of short stature affects the clinical outcome of lower limb lengthening using external fixation. Acta Orthopaedica. April 2014;85(2):181-186.	Not a relevant study design
76	Kitoh H, Kawasumi M, Kaneko H, Ishiguro N. Differential effects of culture-expanded bone marrow cells on the regeneration of bone between the femoral and the tibial lengthenings. Journal of Pediatric Orthopaedics. September 2009;29(6):643-649.	Not a relevant study design
77	Kitoh H, Kitakoji T, Tsuchiya H, Katoh M, Ishiguro N. Distraction osteogenesis of the lower extremity in patients with ACH/hypochondroplasia treated with transplantation of culture-expanded bone marrow cells and platelet-rich plasma. Journal of Pediatric Orthopaedics. September 2007;27(6):629-634.	No paediatric patients with ACH
78	Kitoh H, Mishima K, Matsushita M, Nishida Y, Ishiguro N. Early and late fracture following extensive limb lengthening in patients with ACH and hypochondroplasia. Bone Joint J. Sep 2014;96-B(9):1269-1273.	No paediatric patients with ACH
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197	Shadi M, Koczewski P. Humeral lengthening with a monolateral external fixator in ACH. [Polish]. *Pediatric Endocrinology, Diabetes and Metabolism.* 2007;13(3):121-124.	No relevant intervention for Denmark
198	Song SH, Agashe MV, Huh YJ, Hwang SY, Song HR. Physeal growth arrest after tibial lengthening in ACH. *Acta Orthopaedica.* June 2012;83(3):282-287.	No relevant intervention for Denmark
199	Song SH, Kim SE, Agashe MV, et al. Growth disturbance after lengthening of the lower limb and quantitative assessment of physeal closure in skeletally immature patients with ACH. *Journal of Bone and Joint Surgery - Series B.* April 2012;94 B(4):556-563.	No relevant intervention for Denmark
200	Alonso-Hernandez J, Galan-Olleros M, Miranda-Gorozarri C, Egea-Gamez RM, PalazonQuevedo A. Two-stage Bone Lengthening With Reuse of a Single Intramedullary Telescopic Nail in Patients With ACH. Journal of pediatric orthopedics. 2022;42(6):e616-e22.	No relevant intervention for Denmark
201	Batibay SG, Balci HI, Bayram S, Chodza M, Goksoy S, Hurmeydan OM, et al. Quality of Life Evaluation Following Limb Lengthening Surgery in Patients with ACH. Indian Journal of Orthopaedics. 2020;54(Suppl 1):39-46.	No relevant intervention for Denmark
202	Chen M, Miao H, Liang H, Ke X, Yang H, Gong F, et al. Clinical Characteristics of Short-Stature Patients With Collagen Gene Mutation and the Therapeutic Response to rhGH. Frontiers in Endocrinology. 2022;13((Chen, Miao, Liang, Ke, Yang, Gong, Wang, Duan, Chen, Pan, Zhu) Key Laboratory of Endocrinology of National Health Commission, Department of Endocrinology, State Key Laboratory of Complex Severe and Rare Diseases Peking, Union Medical College Hospital, Ch):820001.	No relevant intervention for Denmark
203	Dossanov B, Trofimchuk V, Lozovoy V, Khmyzov S, Dossanova A, Zhukenov O, et al. Evaluating the results of long tubular bone distraction with an advanced rod monolateral external fixator for ACH. Scientific reports. 2021;11(1):14727.	No relevant intervention for Denmark
204	Egea-Gamez RM, Galan-Olleros M, Alonso-Hernandez J, Miranda-Gorozarri C, MartinezCaballero I, Palazon-Quevedo A, et al. Improvement of the sagittal alignment of the spine in patients with ACH after subtrochanteric femoral lengthening. Spine Deformity. 2022((Egea-Gamez, Gonzalez-Diaz) Spinal Unit, Pediatric Orthopaedic Surgery and Traumatology Department, Hospital Infantil Universitario Nino Jesus, Av. de Menendez Pelayo, 65, Madrid 28009 JCR, Spain(Galan-Olleros, Alonso-Hernandez, Miranda-Gorozarri, Palazon).	No relevant intervention for Denmark

#	Reference	Reason for exclusion
205	Laufer A, Rolfing JD, Gosheger G, Toporowski G, Frommer A, Roedl R, et al. What Are the Risks and Functional Outcomes Associated With Bilateral Humeral Lengthening Using a Monolateral External Fixator in Patients With ACH? Clinical orthopaedics and related research. 2022((Laufer, Rolfing, Toporowski, Frommer, Roedl, Vogt) Pediatric Orthopaedics, Deformity Reconstruction and Foot Surgery, University Hospital Muenster, Muenster, Germany(Rolfing) Children's Orthopaedics and Reconstruction, Aarhus University Hospital, Aarhus).	No relevant intervention for Denmark
206	Song MH, Kim TJ, Chang AS, Song HR. Wire bending development and progression during Ilizarov system tibial lengthening in skeletally immature patients with ACH. Journal of Orthopaedic Translation. 2020;25:73-9.	No relevant intervention for Denmark

13.5 Quality assessment

This review used systematic methods in line with the Cochrane Handbook for Systematic Reviews of Interventions, to conduct an exhaustive search of the literature, identifying evidence relevant to the three review objectives [189]. Multiple electronic databases were searched including MEDLINE, Embase, CDSR, CENTRAL and DARE. Additionally, reference lists of relevant SLRs and (N)MAs were conducted to ensure that any relevant studies that were not identified by the database searches were not missed. ClinicalTrials.gov and other clinical trial registries were searched to ensure that all relevant studies were identified. Conference proceedings from 2018 or later were searched to identify any relevant, high-quality conference research that had not yet been published as a full manuscript, minimising publication bias. Additional supplementary searches of non-European databases and validation searches of a previously-conducted TLR were performed to identify further relevant evidence from relevant markets. Furthermore, articles published in any language were eligible for inclusion. Two reviewers performed each stage of study selection independently, including title/abstract review and full text review, thereby minimising selection bias. Any disagreements were resolved by a third reviewer.

A limitation of the evidence itself could be the small number of RCTs identified. Only one vosoritide RCT (Study 111-301) included a placebo arm. The majority of included studies were either single arm trials or observational studies.

13.6 Unpublished data

Appendix Table 13 lists unpublished vosoritide study reports providing input to this application. All unpublished data included in the application are based on pre-specified analyses of individual patient-level data from the studies. Unpublished data has only been used in the application to the extent that it is considered relevant and is strengthening the basis of evidence for the assessment significantly in terms of efficacy and safety documentation. Therefore, all unpublished data used in the application is considered to be of high quality and validity.

Appendix Table 13. List of unpublished studies from the clinical development program for vosoritide

Data source	ID/Study title	Population	Intervention and comparator
Study 111-901 CSR	111-901: A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with ACH	Pediatric subjects with ACH from birth to ≤ 17 years of age	NA (Observational)
Study 111-501 Observational study report	LIAISE-111-501: The Impact of ACH on Quality of Life, Healthcare Resource Use,	ACH subjects of all ages at participating EU study sites	NA (Observational)

Data source	ID/Study title	Population	Intervention and comparator
	Clinical, Socio-economic and Psychosocial State of the Individual		
Study 111-206/208 CSR interim	111-206: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with ACH, Age 0 to < 60 Months	Infants and young children aged 0–<60 months (5 years) with genetically confirmed ACH Cohort 1: children aged ≥24–<60 months Cohort 2: children aged ≥6–>24 months	Cohort 1: 15 µg/kg/day SC injection (all patients) Cohort 2: 30 µg/kg/day adjusted to 15 µg/kg/day when patients reach 2 years of age compared to placebo

14. Appendix B Main characteristics of included studies

14.1.1 Phase III clinical studies

14.1.1.1 Study 111-301

Appendix Table 14. Main characteristics, study 111-301

Trial name: 111-301	NCT number: NCT03197766 [107]
Objective	Assess vosoritide administered as a therapeutic option for the treatment of children with ACH.
Publications – title, author, journal, year	Savarirayan, R., et al., Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. Lancet, 2020. 396(10252): p. 684-692. [22]
Study type and design	Phase III, randomised, double-blind, placebo-controlled, multi-national, multi-centre trial in patients aged 5–<18 years with documented ACH confirmed by genetic testing. Completed.
Sample size (n)	121
Main inclusion and exclusion criteria	**Inclusion Criteria**: • Parent(s) or guardian(s) consent • 5 to < 18 years old • ACH, documented and confirmed by genetic testing • At least a 6-month period of pretreatment growth assessment in Study 111-901 before study entry • If sexually active, willing to use a highly effective method of contraception • Ambulatory and able to stand without assistance **Exclusion Criteria**: • Hypochondroplasia or short stature condition other than ACH • Have any of the following: Hypothyroidism or hyperthyroidism Insulin-requiring diabetes mellitus Autoimmune inflammatory disease Inflammatory bowel disease Autonomic neuropathy • History of any of the following: Renal insufficiency defined as serum creatinine > 2 mg/dL Chronic anemia Baseline systolic blood pressure (BP) < 70 millimeters of mercury (mm Hg) or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms ie, dizziness, fainting) or recurrent symptomatic orthostatic hypotension

Trial name: 111-301	NCT number: NCT03197766 [107]
	Cardiac or vascular disease • Have a clinically significant finding or arrhythmia on screening electrocardiogram (ECG) that indicates abnormal cardiac function or conduction or Fridericias corrected QTc-F > 450 msec • Have an unstable condition likely to require surgical intervention during the study (including progressive cervical medullary compression or severe untreated sleep apnea) • Decreased growth velocity (< 1.5 cm/yr) over a period of 6 months or evidence of growth plate closure (proximal tibia, distal femur) • Treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the previous 6 months or treatment greater than 6 months at any time • Greater than 1 month treatment with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the previous 12 months • Planned or expected to have limb-lengthening surgery during the study period. Subjects with previous limb- lengthening surgery may enroll if surgery occurred at least 18 months prior to the study and healing is complete without sequelae. • Planned or expected bone-related surgery (ie. surgery involving disruption of bone cortex, excluding tooth extraction), during the study period. Subjects with previous bone-related surgery may enroll if surgery occurred at least 6 months prior to the study and healing is complete without sequelae. • Had a fracture of the long bones or spine within 6 months prior to screening • History of severe untreated sleep apnea • New initiation of sleep apnea treatment (e.g. CPAP or sleep apnea-mitigating surgery) in the previous 2 months prior to screening • History of hip surgery or hip dysplasia atypical for achondroplastic subjects • History of clinically significant hip injury in the 30 days prior to screening • History of slipped capital femoral epiphysis or avascular necrosis of the femoral head • Abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant • Concurrent disease or condition that would interfere with study participation or safety evaluations, for any reason • Condition or circumstance that places the subject at high risk for poor treatment compliance or for not completing the study
Intervention	Daily SC injections of vosoritide 15 µg/kg, n= 60 subjects

Trial name: 111-301	NCT number: NCT03197766 [107]
Comparator(s)	Placebo, n= 61 subjects
Follow-up time	60 weeks (4 weeks screening, 52 weeks of double-blind treatment with 4 weeks safety follow-up)
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary:** Change from baseline in AGV at Week 52. The primary estimand was the difference between the vosoritide group and the placebo group in the mean change from baseline in AGV at the 52-week time point determined from a covariate adjusted ANCOVA model that includes all subjects in the Full Analysis Set (FAS). **Secondary:** Change from baseline at Week 52: ○ in height Z-score ○ in upper to lower segment body ratio ○ in bone metabolism biomarkers: collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP) ○ in QoL as measured by the Quality of Life in Short Stature Youth (QoLISSY) and Paediatric Quality of Life (PedsQL) questionnaires (every 6 months, till completion) ○ in functional independence as measured by WeeFIM • Incidence of Adverse Events in patients treated with vosoritide compared with control patients in the placebo group at 54 weeks **Other endpoints, results not included in this application:** • Change from baseline at week 52 in body proportion ratios of the extremities • bone morphology and pathology by X-ray and dual X-ray absorptiometry (DXA): bone age, bone age Z-score, bone mineral density (BMD), BMD Z-score, and bone mineral content (BMC). • pharmacokinetics (PK) of vosoritide • Immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures • Presence and severity of sleep-disordered breathing overnight by measurement of blood oxygen saturation, pulse rate, and airflow • Biomarkers of vosoritide activity: Urine cyclic guanosine monophosphate (cGMP) normalised by creatinine concentration • Exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signaling
Method of analysis	All efficacy analyses were performed on the Full Analysis Set (FAS) which included all randomised subjects

Trial name: 111-301	NCT number: NCT03197766 [107]
	Analysis of covariance (ANCOVA) models were used to determine the treatment difference between vosoritide and placebo at 52 weeks. Unless otherwise specified, all models included the following baseline covariates: Treatment group, Stratum (Male Tanner Stage I, Female Tanner Stage I, Male Tanner Stage > I, Female Tanner Stage > I), age at baseline, AGV at baseline, Height Z-score at baseline. The following primary hypothesis was tested (two-tailed): H0: Difference in mean AGV change from baseline at Week 52 between vosoritide group and the placebo group = 0 Ha: Difference in mean AGV change from baseline at Week 52 between vosoritide group and the placebo group ≠ 0 The study was considered positive if the two-sided p-value in favour of vosoritide was < 0.05. Results of the statistical analyses were provided in separate tables, including the least-squares (LS) mean change from baseline at Week 52 for each treatment group, the treatment difference in LS means (calculated as vosoritide – Placebo), the 95% confidence interval (CI) for the treatment difference, and corresponding 2-sided p-value. **Primary Analysis** - Change from baseline in AGV (ANCOVA model) Full Analysis Set (FAS): ITT, all randomised, consented subjects included. **Secondary analysis** (pre-specified) – Change from baseline in height Z-score (ANCOVA model). Full Analysis Set. **Other secondary analysis** (pre-specified) – Change from baseline in standing height (ANCOVA model)
Subgroup analyses	Subgroup analyses were conducted on the primary and two key secondary efficacy endpoints and were based on the imputed data described for the primary analysis. Only subgroup categories with sufficient data were analyzed. The ANCOVA model was applied separately for each category within a subgroup (prespecified). Subgroup categories of interest included: • Sex (Male, Female) • Age at Baseline (≥ 5 to < 8, ≥ 8 to < 11, ≥ 11 to < 15, ≥ 15 to < 18 years) • Tanner stage at Baseline (I, > I) • Stratum (Male Tanner Stage I, Female Tanner Stage I, Male Tanner Stage > I, Female Tanner Stage > I) • Baseline Height Z-Score (≤ −6, > −6 to ≤ −5, > −5 to ≤ −4, > −4) • Baseline AGV (≤ 3.5, > 3.5 to ≤ 4.5, > 4.5 cm/year)
Other relevant information	After end of this trial subjects were transferred to Extension trial 111-302

14.1.1.2 Study 111-302

Appendix Table 15. Main characteristics, study 111-302

Trial name: 111-302 (extension of 111-301)	**NCT number: NCT03424018 [108]**
Objective	Assess vosoritide administered as a therapeutic option for the treatment of children with ACH
Publications – title, author, journal, year	Savarirayan R., et al., Safe and persistent growth-promoting effects of vosoritide in children with ACH: 2-year results from an open-label, phase 3 extension study, Genetics in Medicine, 2021 [96]
Study type and design	Phase III, open-label, multi-centre long-term extension trial to evaluate the effect of vosoritide on growth velocity in children with ACH who completed 1 year of vosoritide or placebo treatment in the parent trial 111-301. Ongoing
Sample size (n)	119 enrolled from study 111-301 whereof: • 61 placebo/vosoritide (plc/vos) subjects • 58 vosoritide/vosoritide (vos/vos) subjects
Main inclusion and exclusion criteria	**Inclusion Criteria**: • Must have completed Study 111-301 • Female >= 10 years old or who have begun menses must have a negative pregnancy test at the Baseline Visit and be willing to have additional pregnancy tests during the study • If sexually active, willing to use a highly effective method of contraception while participating in the study • Are willing and able to perform all study procedures • Parent(s) or guardian(s) are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, subjects under the age of majority are willing and able to provide written assent (if required by local regulations or the IRB/IEC) after the nature of the study has been explained and prior to performance of any research-related procedure. Subjects who reach the age of majority in their country while the study is ongoing will be asked to provide their own written consent again upon reaching the legal age of majority. **Exclusion Criteria**: • Permanently discontinued BMN 111 or placebo prior to completion of the 111-301 study • Have a clinically significant finding or arrhythmia on Baseline ECG that indicates abnormal cardiac function • Evidence of decreased growth velocity (<1.5 cm/year) as assessed over a period of at least 6 months or of growth plate closure (proximal tibia, distal femur) through bilateral lower extremity X-rays.

Trial name: 111-302 (extension of 111-301)	NCT number: NCT03424018 [108]
	• Require any investigational agent prior to completion of study period • Current therapy with medications known to alter renal function • Pregnant or breastfeeding or plan to become pregnant during study • Concurrent disease or condition that, in the view of the investigator, would interfere with study participation or safety evaluations, for any reason. • Have a condition or circumstance that, in the view of the investigator, places the subject at high risk for poor treatment compliance or for not completing the study.
Intervention	Daily SC injections of vosoritide 15 µg/kg, n= 119
Comparator(s)	N/A
Follow-up time	Until patients have either reached near-FAH, or for 5 years if near-FAH occurs prior to the end of the 5-year period Data cut-off date: 31 October 2019 for interim analysis/updated 02 November 2020 Estimated completion date: December 2024
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints, results included in this application:** **Primary:** Change from baseline in AGV every year till completion in patients treated with vosoritide compared with patients in the placebo group **Secondary:** Change from baseline at week 52: o in height Z-score o in upper to lower body body segment ratio o in standing height o in body proportion ratios of the extremities o in health-related QoL as measured by the QoL in Short-Statured Youth questionnaire (every 6 months, till completion) o in daily activity performance as measured by Activities of Daily Living questionnaire (every 6 months, till completion) • Incidence, severity and relationship to study drug of all treatment- **Other endpoints, results not included in this application:** • Change from baseline at week 52 in bone metabolism biomarkers: collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP)

Trial name: 111-302 (extension of 111-301)	NCT number: NCT03424018 [108]
	• pharmacokinetics (PK) of vosoritide (every 6 months, till completion) • body proportion ratios of the extremities • Immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures • Bone morphology: bone age, bone age Z-score, bone mineral density (BMD), BMD Z-score, and bone mineral content (BMC) • Exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signaling
Method of analysis	Analysis methods following the same procedure as in study 111-301. Full analysis set: Defined according to the intention-to-treat principle and includes all enrolled subjects with a signed informed consent for 111-302. Analysis of covariance models (ANCOVA) were used to determine the treatment difference between vosoritide and placebo The study was considered positive if the two-sided p-value in favour of vosoritide was < 0.05.95% CI for the treatment difference
Subgroup analyses	N/A subgroups not available in the interim CSR
Other relevant information	

14.1.2 Phase II clinical studies

14.1.2.1 Study 111-202

Appendix Table 16. Main characteristics, study 111-202

Trial name: 111-202	NCT number: NCT02055157 [102]
Objective	To evaluate the safety and tolerability of daily SC injections of vosoritide administered to children 5–14 years of age who have a documented clinical history and a positive genetic test for ACH, administered for a total duration of 24 months divided into two phases: • an initial 6-month phase • an optional 18-month extension phase
Publications – title, author, journal, year	Savarirayan, R., et al., C-Type Natriuretic Peptide Analogue Therapy in Children with ACH. N Engl J Med, 2019. 381(1): p. 25- 35; DOI: 10.1056/NEJMoa1813446 [27]
Study type and design	Paediatric, Phase II, open-label dose-escalation trial. Completed
Sample size (n)	35
Main inclusion and exclusion criteria	**Inclusion Criteria:**

- Parent(s) or guardian(s) are willing and able to provide written, signed informed consent
- 5 to 14 years old at end of study
- ACH, documented by clinical grounds, confirmed by genetic testing
- At least 6-month of pretreatment growth assessment in Study 111-901 before study entry, and one standing height at least 6 months prior to screening for 111-202
- Negative pregnancy test at the Screening Visit for females ≥ 10 years old or who have begun menses
- If sexually active, willing to use a highly effective method of contraception while participating in the study
- Ambulatory, able to stand without assistance
- Willing and able to perform all study procedures as physically possible
- Parents/caregivers willing to administer daily injections to the subjects

Additional inclusion Criteria Optional, Open-label Extension Phase:

- Appropriate written informed consent

Exclusion Criteria:

- Hypochondroplasia or short stature condition other than ACH
- Have any of the following:
  - Hypothyroidism or hyperthyroidism
  - Insulin-requiring diabetes mellitus
  - Autoimmune inflammatory disease
  - Inflammatory bowel disease
  - Autonomic neuropathy
  - Recent acute illness associated with volume dehydration not completely resolved prior to the first dose of study drug
- Unstable condition requiring surgical intervention during the study
- Growth plates have fused
- Have a history of any of the following:
  - Renal insufficiency, defined as creatinine > 2 mg/dl
  - Anemia
  - Baseline systolic BP < 75 mm Hg or recurrent symptomatic hypotension or recurrent symptomatic hypotension, recurrent symptomatic orthostatic hypotension
- Cardiac or vascular disease, including the following:

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  - Cardiac dysfunction (abnormal echocardiogram [ECHO] including left ventricle [LV] mass) at Screening Visit
  - Hypertrophic cardiomyopathy
  - Pulmonary Hypertension
  - Congenital heart disease with ongoing cardiac dysfunction
  - Cerebrovascular disease
  - Aortic insufficiency
  - Clinically significant atrial or ventricular arrhythmias
- Have an ECG showing any of the following:
  - Right or left atrial enlargement or ventricular hypertrophy
  - PR (period of time from the beginning of atrial depolarization until the beginning of ventricular depolarization) interval > 200 msec
  - QRS (The Q, R, and S heart waves that are measured on an electrocardiogram) interval > 110 msec
  - Corrected QTc-F (Measure of the corrected time between the start of the Q wave and end of the T wave in the heart's electrical cycle) > 450 msec
  - Second- or third-degree atrioventricular block
  - Documented Vitamin D deficiency
- Require any investigational agent prior to completion of study period
- Have received another investigational product or investigational medical device within 30 days before the Screening visit
- Use of any other investigational product or investigational medical device for the treatment of ACH or short stature
- Current chronic therapy with antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function
- Treatment with growth hormone, IGF-1 (Insulin-like growth factor), or anabolic steroids in the previous 6 months or long-term treatment (> 3 months) at any time
- Long-term treatment (> 1 month) with oral corticosteroids
- Concomitant medication that prolongs the QT/QTc-F interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
- Pregnant or breastfeeding at the Screening Visit or planning to become pregnant (self or partner) at any time during the study

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Trial name: 111-202	NCT number: NCT02055157 [102]
	• Limb-lengthening or bone-related surgery < 18 months prior to study enrollment • Had a fracture of the long bones or spine within 6 months prior to screening (except for fracture of digits or toes) • AST (Aspartate Transaminase) or ALT (Alanine Transaminase) at least 3x upper limit of normal (ULN) or total bilirubin at least 2x ULN • Evidence of severe sleep apnea requiring surgery or new initiation of CPAP (Continuous positive airway pressure). • History of malignancy and chemotherapy/radiation or currently under work-up for suspected malignancy • Known hypersensitivity to BMN 111 or its excipients • Have a condition or circumstance that, in the view of the Investigator, places the subject at high risk for poor treatment compliance or for not completing the study • Concurrent disease or condition that would interfere with study participation or safety • Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the PI. • Have a history of hip surgery or severe hip dysplasia • Have a history of clinically significant hip injury in the 30 days prior to screening. • History of slipped capital femoral epiphysis or avascular necrosis of the femoral head. • Are unable to lie flat when in prone position Additional Exclusion Criteria for Optional, Open-label Extension Phase: • Use of restricted therapies during the initial 6 months of the study • Permanently discontinued BMN 111 during the initial 6 months of the study
Intervention	Vosoritide Cohort 1: daily morning dose 2.5 µg/kg (n=8) Cohort 2: daily morning dose 7.5 µg/kg (n=8) Cohort 3: daily morning dose 15.0 µg/kg (n=8-10) Cohort 4: daily morning dose 30.0 µg/kg (n=8-10)
Comparator(s)	N/A
Follow-up time	6-24 months
Is the study used in the health economic model?	N/A

Trial name: 111-202	NCT number: NCT02055157 [102]
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary:** Incidence of AEs, SAEs and clinically significant changes in vital signs, physical examination, ECG and echocardiogram results, imaging results, anti-vosoritide immunogenicity evaluations, and laboratory test results (urine, chemical and haematology analysis). **Secondary:** Change from baseline at 6-months: • In AGV • In height Z-score using (CDC Reference) • In body proportions **Other endpoints, results not included in this application:** • PK profile • biomarkers of drug activity (cGMP) • bone metabolism biomarkers: collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP) • QCT bone mineral density (BMD) • growth plate morphology morphology through anterior-posterior (AP) lower extremity X-ray • sleep apnea • elbow joint range of motion • immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures
Method of analysis	The efficacy analysis was performed during the initial 6- month period and over the entire efficacy population study period. Baseline AGV was established based on the results of the observational study AGV, based on standing height measurements every 6 months, was presented using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Testing for the hypothesis of no variation from baseline of AGV was performed using a paired t-test during the initial 6-month period and the p-value was considered descriptive. The variation in body proportion ratios (upper arm/forearm length ratio, upper leg length/lower leg length ratio, and upper/lower body segment ratio) compared to baseline at each scheduled assessment point was presented at 6 months. The height measurement was converted to SDS, also known as Z-Score, by comparison with reference values of children of the same stature in the CDC database. The Z-Score was presented similarly to the AGV. Results were presented by Cohort and for all Cohorts. Safety was assessed based on the incidence, degree of severity, and relationship to study treatment of all AEs reported during the study.

Trial name: 111-202	NCT number: NCT02055157 [102]
	Other safety measures, including clinical biology results, vital signs, ECG and ECHO values were evaluated. Baseline values for tolerance parameters were defined by the last non-missing assessment before the first dose of treatment. The numerical parameters were presented by descriptive statistics (number n of patients, mean, standard deviation, median, minimum and maximum). Adverse events were presented as number and percentage. AGV, based on standing height measurements every 6 months, was presented using descriptive statistics (mean, standard deviation, median, minimum, and maximum). The analysis populations were as follows (in the corresponding periods, initial period and extension period): - Tolerance population, including all patients who received at least one dose of vosoritide during the period. - Efficacy population, including all patients who received at least one dose of vosoritide and presenting data for at least one efficacy endpoint evaluated. - Pharmacokinetic population, including all patients in the vosoritide group who received at least one treatment dose and with at least one evaluable pharmacokinetic parameter during the period.
Subgroup analyses	No subgroups were determined for assessment of efficacy or safety on this study.
Other relevant information	

14.1.2.2 Study 111-205

Appendix Table 17. Main characteristics, study 111-205

Trial name: 111-205 (Extension of 111-202)	NCT number: NCT02724228 [103]
Objective	To evaluate the long-term safety and tolerability of daily subcutaneous injections of vosoritide in children with ACH who have completed 2 years of treatment in the 111-202 study
Publications – title, author, journal, year	Hoover-Fong J., et al. Vosoritide for Children with ACH: A 60-month update from an ongoing Phase 2 clinical trial, presented at the ACMG Annual Clinical Genetics Meeting: April 13–16, 2021 [93]
Study type and design	Phase II, open-label, extension study of 111-202 dose-finding study
Sample size (n)	30
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Have completed 24 months of BMN 111 treatment in Study 111-202. • Parent(s) or guardian(s) are willing and able to provide written, signed informed consent. Subjects under the age of majority are willing and able to provide written assent (if required). Subjects who reach the age of majority in their country will be asked to

Trial name: 111-205 (Extension of 111-202)	NCT number: NCT02724228 [103]
	provide their own written consent upon reaching the legal age of majority. • If sexually active, willing to use a highly effective method of contraception while participating in the study. • Females >= 10 years old or who have started menses must have a negative pregnancy test at baseline and be willing to have additional pregnancy tests during the study • Willing and able to perform all study procedures as physically possible • Parents/caregivers willing to administer daily injections to the subjects and complete the required training. **Exclusion Criteria**: • Requires any investigational agent prior to completion of study period. • Have a condition or circumstance that, in the view of the Investigator, places the subject at high risk for poor treatment compliance or for not completing the study. • Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations for any reason. • Permanently discontinued BMN 111 during the 111-202 study. • Subject is pregnant at Baseline visit or planning to become pregnant (self or partner) at any time during the study. • Current chronic therapy with restricted medications.
Intervention	Vosoritide Cohort 1: daily morning dose 2.5 µg/kg (n=6) Cohort 2: daily morning dose 7.5 µg/kg (n=6) Cohort 3: daily morning dose 15.0 µg/kg (n=10) Cohort 4: daily morning dose 30.0 µg/kg (n=8)
Comparator(s)	N/A
Follow-up time	For a minimum of 5 years or until near final adult height is reached whichever occurs later. Estimated completion date: October 2022
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary:** • Incidence, severity, and relationship to study drug of all treatment-emergent adverse events.

Trial name: 111-205 (Extension of 111-202)	NCT number: NCT02724228 [103]
	Secondary: • Change from baseline in AGV in cm/year (interval and cumulative) • Change from baseline in height Z-score • Change from baseline in upper to lower body segment ratio **Other endpoints, results not included in this application:** • Long-term dose exposure profile and immunogenicity of vosoritide to assess for impact on safety, PK, and efficacy measures • QCT bone mineral density (BMD) • Growth plate morphology through anterior-posterior (AP) lower extremity X-ray • Long-bone growth, and morphology of the spine • Sleep apnea • Elbow joint range of motion • bone metabolism and vosoritide pharmacodynamics biomarkers: Collagen X biomarker, bone-specific alkaline phosphatase (BSAP), pro-collagen type 1 N-terminal pro-peptide, cyclic GMP
Method of analysis	Statistical methods: Analysis populations: Full Analysis Set (FAS): All enrolled subjects with a signed informed consent for 111-205. Safety Population: All subjects in the FAS who receive at least one dose of the study drug in 111-205. PK Population: All subjects in the Safety Population who have at least one evaluable PK concentration in 111-205. Immunogenicity Population: All subjects in the Safety Population who have at least one evaluable immunogenicity sample in 111-205. Efficacy Analyses: All efficacy endpoints are assessed on the FAS population by the Cohort into which they were enrolled into in 111-202. AGV is summarized by 12-month intervals and cumulatively from baseline.
Subgroup analyses	Data for pre-specified subgroup analysis performed for the key efficacy endpoints of by: • Sex (Male, Female) • Age-group at baseline (≥ 5 to < 8, ≥ 8 to < 11, ≥ 11 to < 15, ≥ 15 to < 18 years) • Baseline height Z-Score (≤ −6, > −6 to ≤ −5, > −5 to ≤ −4, > −4) • Baseline AGV (≤ 3.5, > 3.5 to ≤ 4.5, > 4.5
Other relevant information	

14.1.2.3 Study 111-206

Appendix Table 18. Main characteristics, study 111-206

Trial name: 111-206	NCT number: NCT03583697[104]
Objective	To assess the safety and tolerability of vosoritide in patients 0 to <60 months with ACH and to assess the efficacy of vosoritide on the change in the height/length Z-score
Publications – title, author, journal, year	A randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia. Poster presented at the Endocrine Society's 2022 Annual Meeting, June 11-14, 2022, Atlanta, GA, Savarirayan et al., 2022 [94]
Study type and design	Phase II, multicenter, randomized, double-blind, placebo-controlled study lasting 60 weeks (52 weeks of treatment). Patients were included in three age Cohorts based on their age when screening the study. Cohort 1: patients aged ≥ 24 to <60 months (n ≥ 30 in total: 3 sentinel patients who received vosoritide, and at least 27 additional patients randomized at a 1: 1 ratio to the vosoritide or placebo groups), stratified by age (≥ 24 to <36 months and ≥ 36 months to <60 months). Cohort 2: patients aged ≥ 6 to <24 months (n ≥ 20 in total: 3 sentinel patients who received vosoritide and at least 17 additional patients randomized at a 1: 1 ratio in the vosoritide or placebo groups), stratified by age (≥ 6 months to <15 months and ≥ 15 months to <24 months). Cohort 3: children aged 0 to <6 months (n ≥ 20 in total: 3 sentinel patients who received vosoritide and at least 17 additional patients randomized at a 1: 1 ratio to vosoritide or placebo). Treatment was initiated between ≥ 3 months and <6 months after 3 months of observation. At the data cutoff for the interim study report, inclusions in Cohort 3 had not yet started. Patients were randomized (allocation ratio 1: 1) to receive: Vosoritide group: - Vosoritide by the subcutaneous route: 15 µg/kg/day (Cohort 1), 15 µg/kg/day and 30 µg/kg/day (Cohort 2). Placebo group: - Placebo by subcutaneous route.
Sample size (n)	75
Main inclusion and exclusion criteria	**Inclusion Criteria**: • Diagnosis of ACH, confirmed by genetic testing • Age 0 to < 60 months at study entry (Day 1) • At least 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry (Cohort 1 & 2) or at least 3 months of observation prior to treatment (Cohort 3) **Exclusion Criteria:** • Have hypochondroplasia or short-stature condition other than ACH (e.g., trisomy 21, pseudoACH, etc.) • Have any of the following: ○ Hypothyroidism or hyperthyroidism

Trial name: 111-206	NCT number: NCT03583697[104]
	○ Insulin-requiring diabetes mellitus ○ Autoimmune inflammatory disease (including celiac disease, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, etc.) ○ Inflammatory bowel disease ○ Autonomic neuropathy • Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening ECG • Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator and informed by the following assessments: ○ Physical exam (eg, neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins) ○ Polysomnography (eg, severe central sleep apnea) ○ MRI indicating presence of severe CMC or spinal cord damage • Subject weight < 5.0 kg (Cohort 1 & 2) or < 4.0 kg (Cohort 3) • Treatment with growth hormone within 6-months prior to screening or prolonged treatment (> 3 months) at any time • Any history of spine or long-bone surgery or any bone-related surgery with chronic complications • Any history of limb-lengthening surgery or planned limb-lengthening during the study • Fracture of the long bones within 6 months prior to screening
Intervention	Vosoritide Cohort 1: 15 µg/kg/day SC injection (all patients) Cohort 2: 30 µg/kg/day adjusted to 15 µg/kg/day when patients reach 2 years of age
Comparator(s)	Placebo
Follow-up time	52 weeks Estimated completion date: February 2022
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary:** • Z-Score for height/length at 52 weeks. **Secondary:**

Trial name: 111-206	NCT number: NCT03583697[104]
	• Tolerance and tolerability: adverse event (AE), serious adverse event (SAE), clinically significant variation in vital signs, clinical examination, electrocardiogram (ECG), results of imaging and laboratory tests (urine, chemical, hematologic). • AGV at week 52 **Other endpoints, results not included in this application:** • Evaluation of the effect of vosoritide on bone morphology by bilateral radiographs of the lower limbs, radiographs of the lumbar spine and DXA of the whole body and spine. • Pharmacokinetic parameters • Evaluation of hip function by clinical examination • Assessment of pain in the hip, thigh or knee, or a change in gait. • Assessment of patients' quality of life, state of development, and functional independence using an age-specific quality of life questionnaire and functional independence/quality of life questionnaires (Bayley-III, WeeFIM, and ITQOL and CBCL scores). • Immunogenicity parameters (total anti-vosoritide antibody - TAb, cross-reactivity of anti-vosoritide antibodies with endogenous CNP, ANP and BNP (TAb) and neutralizing anti-vosoritide antibody (NAb). • Bone metabolism parameters and pharmacodynamic biomarkers of vosoritide (CXM and bone-specific alkaline phosphatase, type II collagen (CTX-II), cyclic guanosine monophosphate (cGMP)). • Evaluation of the effect of vosoritide on growth and body proportions: anthropometric measurements, ratio between upper and lower body segments, ratio of the length of the upper arm to the length of the lower arm (forearm), ratio upper leg length (thigh) to knee/heel length, ratio upper leg length (thigh)/tibial length, ratio between arm span and waist when standing. • Effect on sleep apnea (sleep study to assess the presence and severity of sleep breathing disorders by measuring blood oxygen saturation, and air flow by night monitoring, apnea/hypopnea index). • Magnetic resonance imaging (MRI) to define cranial and cerebral morphology. • Concomitant procedures, interventions and surgeries. • Exploratory genomics including, but not limited to, NPR-2, BRAF, and other genes associated with CNP signaling
Method of analysis	**Efficacy assessment** Efficacy data were analyzed using descriptive statistics. Primary endpoint analysis: Height Z-score Each standing height measurement was converted into a standard deviation score (SDS), called a Z-score, adapted for age and sex by comparison with the

Trial name: 111-206	NCT number: NCT03583697[104]
	reference data available in children of average height of the year Of the Center for Disease Control (CDC). Height Z-Score and its changes from baseline were presented at Week 26 and Week 52 for sentinel patients, by Cohort and in total. Analysis of the secondary endpoints of the study: The AGV and other anthropometric measures (ratio of upper and lower body segments, standing and sitting height, head circumference, etc.) were summarized similarly to the Z-Score for height and assessed for variations from baseline. For the youngest patients, body length was measured and used in analyzes instead of standing height. **Tolerance assessment** Safety was assessed on the basis of the incidence, degree of severity and likely correlation with treatment for adverse events reported during the study. Other safety measures including laboratory results, vital signs, ECG and echocardiogram values were evaluated. Unless otherwise specified, inclusion tolerance parameters were defined as the last non-missing assessment before the first dose. Numerical parameters were described using descriptive statistics including number (n), mean, standard deviation (SD), median, minimum and maximum. **Analysis populations** The analysis populations were as follows: - "Full analysis set" (FAS) population, defined according to the principles of the intention-to-treat population. This population includes all sentinel patients and randomized patients. FAS was used to present baseline characteristics and efficacy data. - Safety population, subset of the Full Analysis Set (FAS) population, includes patients who received at least one dose of vosoritide or placebo in this study. The tolerance population was used to present the safety data.
Subgroup analyses	No subgroup analyses are available at present for Study 111-206
Other relevant information	

14.1.2.4 Study 111-208

Appendix Table 19. Main characteristics, study 111-208

Trial name: 111-208 (extension study to 111-206)	NCT number: NCT03989947[105]
Objective	To evaluate the safety and efficacy of vosoritide in children with ACH who complete 111-206, until they reach near adult final height
Publications – title, author, journal, year	No publication yet
Study type and design	**Currently enrolling**

Trial name: 111-208 (extension study to 111-206)	NCT number: NCT03989947[105]
	Phase II, multicentre, open-label long-term extension trial. All patients who completed Study 111-206 in each of the treatment groups were eligible to receive vosoritide in the open-label extension study, to assess the safety and long-term efficacy of treatment with vosoritide (111-208). For patients included in the extension study, the safety follow-up visit at week 56 was canceled. Patients were included in three age Cohorts based on their age when screening the study: Cohort 1: patients aged ≥ 24 to <60 months, Cohort 2: patients aged ≥ 6 to <24 months, Cohort 3: children aged 0 to <6 months The patients included in study 11-208 were followed until reaching the final adult height (NFAH, Near Final Adult Height) defined by the demonstration of the closure of the growth plate and a AGV value <1, 5 cm/year. Patients were randomized (allocation ratio 1: 1) to receive Vosoritide or placebo Patients were included in three age Cohorts based on their age when screening the study.
Sample size (n)	70
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Must have completed Study 111-206 on investigational treatment (BMN 111 or placebo). • Parent(s) or guardian(s) are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to performance of any research related procedure. Also, subjects under the age of majority are willing and able to provide written assent (if required by local regulations or the IRB/IEC) after the nature of the study has been explained and prior to performance of any research-related procedure. Subjects who reach the age of majority in their country while the study is ongoing will be asked to provide their own written consent again upon reaching the legal age of majority. • Are willing and able to perform all study procedures **Exclusion Criteria:** • Permanently discontinued BMN 111 or placebo prior to completion of Study 111-206 • Have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or QTc-F > 450 msec • Require any investigational agent (except BMN 111) prior to completion of study period • Current therapy with antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, GnRH agonists, any medication that may impair or enhance compensatory

Trial name: 111-208 (extension study to 111-206)	NCT number: NCT03989947[105]
	tachycardia, diuretics, or other drugs known to alter renal or tubular function • Pregnant or planning to become pregnant (self or partner) at any time during the study • Concurrent disease or condition that, in the view of the investigator, would interfere with study participation or safety evaluations, for any reason • Have a condition or circumstance that, in the view of the investigator, places the subject at high risk for poor treatment compliance
Intervention	Vosoritide Cohort 1: 15 µg/kg/day SC injection (all patients) Cohort 2: 30 µg/kg/day adjusted to 15 µg/kg/day when patients reach 2 years of age
Comparator(s)	N/A
Follow-up time	Until patients reach near adult final height Estimated completion date: December 2026
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Study is currently enrolling, and no results will be presented in this application** **Endpoints:** **Primary:** • Adverse events (AEs), SAEs, and clinically significant changes in vital signs, physical examination, electrocardiogram (ECG), imaging, and laboratory test results (urinalysis, chemistry, haematology). • Length/height Z-score at Week 52. **Secondary:** • AGV measures • Upper to lower segment body ratio and proportion ratios of the extremities • Bone metabolism biomarkers: collagen X biomarker (CXM) and bone-specific alkaline phosphatase (BSAP) • QoL, developmental status, and functional independence using age-specific questionnaires including Bayley III, WeeFIM (Functional Independence Measure), infant toddler quality of life (ITQoL), child behaviour checklist (CBCL) **Other endpoints:**
Method of analysis	
Subgroup analyses	No subgroup analyses are available at present for Study 111-208.

Trial name: 111-208 (extension study to 111-206)	NCT number: NCT03989947[105]
Other relevant information	Currently enrolling

14.1.2.5 Study 111-209

Appendix Table 20. Main characteristics, study 111-209

Trial name: 111-209	NCT number: NCT04554940 [106]
Objective	To evaluate Safety of vosoritide in at-risk infants with ACH
Publications – title, author, journal, year	Savarirayan R, Irving M, Maixner W, Thompson D, Offiah AC, Connolly DJ, Raghavan A, Powell J, Kronhardt M, Jeha G, Ghani S, Fisheleva E, Day JR. Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with ACH at risk of requiring cervicomedullary decompression surgery. Sci Prog. 2021 Jan-Mar;104(1):368504211003782. doi: 10.1177/00368504211003782. [95] (Methods and study design)
Study type and design	Ongoing randomized, Controlled, Open-label Clinical Trial With an Open-label Extension to Investigate the Safety of Vosoritide in Infants and Young Children With ACH at Risk of Requiring Cervicomedullary Decompression Surgery.
Sample size (n)	Estimated to 20
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research related procedure. • Have ACH, documented by genetic testing. • Are willing and able to perform all study procedures as physically possible. • Age 0 to ≤ 12 months, at study entry (Day 1). Given that any potential impact of vosoritide therapy on the foramen magnum is dependent on treating as early as possible and as long as possible while the synchondroses at the base of the skull are still open. For subjects > 6 months of age at enrollment, a discussion between the investigator and the Medical Monitor should occur with the goal of limiting the number of subjects in the range of > 6 months to ≤ 12 months of age. • Parent(s) or caregiver(s) are willing to administer daily injections to the subject and complete the required training. • Have evidence of CMC that "may" require surgical intervention **Exclusion Criteria:** • Have hypochondroplasia or short-stature condition other than ACH (eg, trisomy 21, pseudoACH, etc). • Have CMC that either does not require surgical intervention (for example foramen magnum narrowing with preservation of the

Trial name: 111-209	NCT number: NCT04554940 [106]
	cerebrospinal fluid space) or does require immediate surgical intervention . • Have any of the following: Untreated congenital hypothyroidism or maternal history of hyperthyroidism, Insulin-requiring neonatal diabetes mellitus, Autoimmune inflammatory disease, Inflammatory bowel disease, Autonomic neuropathy. • Have a history of any of the following:Renal insufficiency, Chronic anemia,Baseline systolic blood pressure below age and gender specified normal range or recurrent symptomatic hypotension (defined as episodes of low blood pressure generally accompanied by symptoms eg, pallor, cyanosis, irritability, poor feeding) and Cardiac or vascular disease. • Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F ≥ 450 msec on screening ECG. • Have been treated with growth hormone, insulin-like growth factor 1, or anabolic steroids in the 6 months prior to Screening, or long-term treatment (> 3 months) at any time. • Have ever had prior cervicomedullary decompression surgery. • Have had a fracture of the long bones or spine within 6 months prior to Screening.
Intervention	Vosoritide + Standard of Care (standard of care treatment for cervicomedullary compression and once daily subcutaneous injection of vosoritide at 30µg/kg (ages 0 - <2 years old) or 15 µg/kg (ages >2 years old))
Comparator(s)	No Intervention: Standard of Care Alone (institutional standard of care monitoring and treatment for cervicomedullary compression)
Follow-up time	260 weeks Estimated completion date: December 2026
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints:** Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability] Evaluate the effect of Vosoritide on total foramen magnum volume (in cm3) by MRI volumetric measurement software
Method of analysis	
Subgroup analyses	
Other relevant information	

14.1.3 Natural History studies

14.1.3.1 Study 111-901

Appendix Table 21. Main characteristics, study 111-901

Trial name: 111-901 (Natural History Study)	**NCT number: NCT01603095 [99]**
Objective	To collect baseline growth measurements on paediatric patients with ACH – Natural History Study
Publications – title, author, journal, year	Growth parameters in children with achondroplasia: A 7-year, prospective, multinational, observational study. Savarirayan R., et al., Genetics in Medicine, 2022 [98]
Study type and design	Ongoing. A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with ACH being considered for subsequent enrolment in future studies by BioMarin. Enrolled subjects underwent growth measurements at baseline and then subsequently at 3-month intervals until completion of the study (reaching the end of the protocol or enrollment in another BioMarin study), discontinuation of participation, or termination of the study. Subjects who did not enroll in a subsequent BioMarin drug-treatment study could choose to continue participating in Study 111-901 for up to 7 years.
Sample size (n)	363
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, willing and able to provide written assent (as needed) after the nature of the study has been explained and prior to performance of any research-related procedure. • Aged 0 to <= 17 years, inclusive, at study entry. • Have ACH, documented by clinical diagnosis • Are ambulatory and able to stand without assistance (not applicable for infants) • Are willing and able to perform all study procedures as physically possible. **Exclusion Criteria:** • Have hypochondroplasia or short stature condition other than ACH (e.g., trisomy 21, pseudoACH) • Have any of the following disorders: Hypothyroidism Insulin-requiring diabetes mellitus Autoimmune inflammatory disease Inflammatory bowel disease

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Autonomic neuropathy

- Have an unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression
- Growth plates have fused
- Have a history of any of the following:

  Renal insufficiency

  Anemia
- Cardiac or vascular disease, including the following:

  Cardiac dysfunction (abnormal echocardiogram [ECHO] including left ventricle [LV] mass) at Screening Visit

  Hypertrophic cardiomyopathy

  Congenital heart disease

  Cerebrovascular disease, aortic insufficiency

  Clinically significant atrial or ventricular arrhythmias
- Current treatment with antihypertensive medications angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, any medication that may impair or enhance compensatory tachycardia, drugs known to alter renal function that is expected to continue for the duration of the study
- Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the previous 6 months or long-term treatment (> 3 months) at any time
- Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable)
- Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
- Have used any other investigational product or investigational medical device for the treatment of ACH or short stature
- Have had bone-related surgery or expected to have bone-related surgery during the study period. Subjects with previous limb-lengthening surgery may enroll if surgery occurred at least 18 months prior to the study and healing is complete without sequelae.
- Have any condition that, in the view of the Investigator, places the patient at high risk of poor compliance with the visit schedule or of not completing the study.

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Trial name: 111-901 (Natural History Study)	NCT number: NCT01603095 [99]
	• Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation
Intervention	No study drug was administered
Comparator(s)	N/A
Follow-up time	Up to 7 years
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** As this was an observational study to characterize baseline growth data, variables assessed in this study were not categorized as safety or efficacy **Primary objective:** to collect baseline growth measurements on paediatric patients with ACH, including: • Annual Growth Velocity (AGV) • Height Z-Score • Standing or sitting height • Upper to lower body segment ratio • Other body proportion and growth measures **Other endpoints:** • Health related quality of life (HRQoL) and functional independence and activities of daily living (ADL) questionnaires: Pediatric Quality of Life Inventory (PedsQL), Quality of Life in Short Statured Youth (QoLISSY), Functional Independence Measure (WeeFIM)® • Adverse Events **Other endpoints, results not included in this application:** • Child Behavior Checklist (CBCL), Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), Infant Toddler Quality of Life Questionnaire (ITQoL). • Vital signs, physical examination, concomitant medications • bone metabolism biomarkers (bone-specific alkaline phosphatase [BSAP] and collagen X biomarker [CXM]) • genomic, and exploratory biomarkers, 25-hydroxy vitamin D, alkaline phosphatase (ALP) • pulse oximetry (optional) and ACH-related symptoms, tests, and interventions
Method of analysis	All 363 subjects were included in the full analysis set (FAS). Anthropometric measures (of body dimension, size and shape) were collected at approximately the same time at each scheduled visit (±2 hours) by a trained study staff member. Anthropometric measurements were taken in triplicate with the exception of weight, which was taken once. Standardized measuring equipment and detailed measurement techniques were used [25].

Trial name: 111-901 (Natural History Study)	NCT number: NCT01603095 [99]
	The scores in HRQoL questionnaires, and functional independence and ADL questionnaires (including PedsQL, QoLISSY, WeeFIM, CBCL, BSID-III, and ITQoL) were summarized by age at the time of the assessment [25].
Subgroup analyses	
Other relevant information	

14.1.3.2 Study 111-501

Appendix Table 22. Main characteristics, study 111-501

Trial name: 111-501	NCT number: NCT03449368 [190]
Objective	The Impact of ACH on Quality of Life, Healthcare Resource Use, Clinical, Socio-economic and Psychosocial State of individuals with ACH in Europe (Lifetime Impact of ACH Study in Europe (LIAISE))
Publications – title, author, journal, year	Lifetime impact of achondroplasia study in Europe (LIAISE): findings from a multinational observational study. Maghnie M, et al., Orphanet Journal of Rare Diseases, 2023 [97]
Study type and design	Observational, retrospective, cross-sectional in patients with ACH aged 5 years and older in Sweden, Germany, Spain, Italy, Austria and Denmark.
Sample size (n)	Enrolled: 196 patients; Full-Analysis Set: 186 (Austria: n=4; Denmark: n=10; Germany: n=61; Italy: n=59; Spain: n=42; Sweden: n=9; missing: n=1) Completed: 184 patients
Main inclusion and exclusion criteria	**Inclusion Criteria:** 1. Individuals with a documented diagnosis of ACH based on: a. Genetic confirmation of ACH and/or b. Clinical diagnosis of ACH (clinical examination or radiological assessment) 2. ≥ five years of age at the time of enrolment 3. Has the cognitive and linguistic capacities necessary to complete questionnaires in the language of his/her country (and/or parents/legally acceptable representatives, as applicable) 4. Agrees to participate in the study and has read, understood, completed and signed: a. Informed Consent Form (ICF) - for adult subjects b. Informed Assent Form (IAF) - for minor subjects, accompanied by a parental ICF completed by their parents/legally acceptable representatives. The age at which the minor subjects sign the IAF will be subject to local requirements. 5. Has medical records available for at least the five years prior to the date of enrolment.

Trial name: 111-501	NCT number: NCT03449368 [190]
	Exclusion Criteria: 1. Currently participating, or participated within the last six months, in a. a clinical trial of a medicinal product or medical device or, b. other non-clinical, low interventional studies 2. Currently participating or participated in any BioMarin study at any time.
Intervention	No study drug was administered
Comparator(s)	N/A
Follow-up time	26 months
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Standing height, PedsQoL, QoLISSY, WeeFIM, **Other endpoints, results not included in this application:** Healthcare resource use
Method of analysis	Main Summary Measures: • Descriptive summaries of continuous variables included the number of observations available, number of missing data points, mean, SD, median, ranges (minimum and maximum), and 95% CI of the mean and/or inter-quartile ranges (quartiles 1 and 3) when appropriate • Descriptive summaries of categorical variables included the number of observations available, number of missing data points, frequency, and percent. Percentages were based on the number of observations available unless otherwise stated Analysis Populations: • The FAS included all consented patients with a documented diagnosis of ACH per the inclusion Electronic case report form (eCRF) page and historical data available The modified FAS included all patients in the FAS who had at least one non-missing QoL assessment and met the remaining eligibility criteria per the inclusion eCRF page
Subgroup analyses	
Other relevant information	

15. Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

15.1 Baseline patient characteristics

The comparative analyses included comparisons between the vosoritide group (consisting of several treatment groups from studies 111-202/205 and 111-301) and the external control group (untreated ACH subjects from the NH sources).

Appendix Table 23. Baseline characteristics of patients in study 111-202

Characteristic Variable	111-202 (Analysis population: Safety)				
	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)	All Cohorts (N=35)
Age (years), mean (SD) at screening					
Age, n (%) [a]	7.3 (1.58)	8.3 (2.19)	8.0 (1.63)	6.9 (1.17)	7.6 (1.68)
≥ 5 to < 8 years	6 (75.0)	3 (37.5)	4 (40.0)	5 (55.6)	18 (51.4)
≥ 8 to < 11 years	1 (12.5)	1 (12.5)	4 (40.0)	4 (44.4)	10 (28.6)
≥ 11 to < 15 years	1 (12.5)	4 (50.0)	2 (20.0)	0	7 (20.0)
≥ 15 to < 18 years	0	0	0	0	0
Gender, n (%)					
Male	3 (37.5)	5 (62.5)	4 (40.0)	4 (44.4)	16 (45.7)
Female	5 (62.5)	3 (37.5)	6 (60.0)	5 (55.6)	19 (54.3)
White	7 (87.5)	6 (75.0)	5 (50.0)	6 (66.7)	24 (68.6)
Asian	0	1 (12.5)	3 (30.0)	3 (33.3)	7 (20.0)
Black or African American	1 (12.5)	0	1 (10.0)	0	2 (5.7)
Multiple	-	-	-	-	-
Japanese	-	-	-	-	-
Other	0	1 (12.5)	1 (10.0)	0	2 (5.7)
Ethnicity, n (%)[a]					

Characteristic Variable	111-202 (Analysis population: Safety)				
	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)	All Cohorts (N=35)
Not Hispanic or Latino	8 (100.0)	8 (100.0)	9 (90.0)	7 (77.8)	32 (91.4)
Hispanic or Latino	0	0	1 (10.0)	1 (11.1)	2 (5.7)
Not Reported	0	0	0	1 (11.1)	1 (2.9)
Tanner Stage [b], n (%)					
I	-	-	-	-	-
>I	-	-	-	-	-
Not Done					
Breast Tanner stage (Female only)					
I	5 (100.0)	3 (100.0)	6 (100.0)	5 (100.0)	19 (100.0)
Genitalia Tanner stage (Male only)					
I	2 (66.7)	5 (100.0)	4 (100.0)	4 (100.0)	15 (93.8)
Not done	1 (33.3)	0	0	0	1 (6.3)
Weight (kg), n, mean (SD)	18.58 (2.22) (Analysis Population: Efficacy, n=8)	22.50 (4.10) (Analysis Population: Efficacy, n=8)	25.13 (5.74) (Analysis Population: Efficacy, n=10)	19.59 (2.86) (Analysis Population: Efficacy, n=8)	21.56 (4.70)
BMI (kg/m^2), n, mean (SD)	20.13 (2.09)	21.78 (2.10)	22.21 (2.69)	20.44 (1.04)	21.17 (2.18)

Source: BioMarin 2018. Clinical Study Report: 111-202 [31]

Appendix Table 24. Baseline characteristics of patients in study 111-206

Characteristics	Cohort 1 (Sentinel) (n=4) (Age ≥24 to <60 months)		Cohort 2 (Sentinel) (n=4) (Age ≥6 to <24 months)		Overall (N=8)	
	Sentinel (n=4)	Randomised (n=26)	Sentinel (n=4)	Randomised (n=10)	Sentinel (N=8)	Randomised (N=36)
Age at Day 1 months, mean (SD)	48.45 (13.28)	42.63 (11.33)	15.79 (4.02)	17.62 (5.31)	32.12 (19.68)	35.68 (15.10)
Sex, n (%)*						
Male	3 (75.0)	12 (46.2)	4 (100.0)	6 (60.0)	7 (87.5)	18 (50.0)
Female	1 (25.0)	14 (53.8)	0	4 (40.0)	1 (12.5)	18 (50.0)
Race, n (%)*						
White	4 (100.0)	21 (80.8)	3 (75.0)	8 (80.0)	7 (87.5)	29 (80.6)
Asian	0	4 (15.4)	0	1 (10.0)	0	5 (13.9)
Other	0	4 (15.4)	0	1 (10.0)	0	5 (13.9)
Native Hawaiian/Pacific Islander	0	0	0	1 (10.0)	0	1 (2.8)
Multiple	0	1 (3.8)	1 (25.0)	0	1 (12.5)	1 (2.8)
Ethnicity, n (%)*						
Not Hispanic or Latino	4 (100.0)	23 (88.5)	4 (100.0)	9 (90.0)	8 (100.0)	32 (88.9)
Hispanic or Latino	0	2 (7.7)	0	0	0	2 (5.6)
Not Reported	0	1 (3.8)	0	1 (10.0)	0	2 (5.6)
Weight, kg, mean (SD)	14.30 (0.50)	13.81 (3.40)	9.37 (0.44)	9.18 (1.87)	11.83 (2.67)	12.53 (3.69)
Weight Z-Score, mean (SD)	-1.08 (1.09)	-1.13 (1.41)	-0.98 (0.35)	-1.31 (1.05)	-1.03 (0.75)	-1.18 (1.31)
BMI, kg/m2, mean (SD)	20.85 (2.49)	21.27 (2.50)	20.94 (0.70)	19.42 (1.66)	20.90 (1.69)	20.75 (2.43)
BMI Z-Score, mean (SD) (n)	2.79 (0.98) (4)	2.65 (0.98) (26)	NA (NA) (0)	NA (NA) (0)	2.79 (0.98) (4)	2.65 (0.98) (26)

Percentages were calculated using the total number of patients in the full analysis set (N for each treatment group) as the denominator. Abbreviations; max: maximum; min: minimum; SD: standard deviation.
Source: BioMarin Pharmaceutical Inc. Interim CSR 111-206, Table 14.1.6.1[29]

Appendix Table 25. Baseline characteristics of patients in study 111-208

	Age at day 1 of Vosoritid[a] (months)				
Feature	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6	Total N=73
Age at day 1 of study medication[a] (months)					
n	11	22	34	6	73
Mean (SD)	5,41 (0,56)	17,60 (4,08)	42,30 (10,11)	69,55 (2,53)	31,54 (19,77)
Median	5,65	17,95	42,46	70,51	28,12
Min; Max	4,5; 5,9	8,7; 23,4	25,4; 59,8	66,0; 72,0	4,5; 72,0
Gender, n (%)[b]					
Male	5 (45,5)	11 (50,0)	19 (55,9)	2 (33,3)	37 (50,7)
Female	6 (54,5)	11 (50,0)	15 (44,1)	4 (66,7)	36 (49,3)
Ethnicity, n (%)[b]					
White	6 (54,5)	17 (77,3)	23 (67,6)	5 (83,3)	51 (69,9)
Asian	3 (27,3)	4 (18,2)	9 (26,5)	1 (16,7)	17 (23,3)
Other	2 (18,2)	3 (13,6)	4 (11,8)	0	9 (12,3)
Japanese	1 (9,1)	1 (4,5)	5 (14,7)	1 (16,7)	8 (11,0)
Other	1 (9,1)	1 (4,5)	1 (2,9)	0	3 (4,1)
Native Hawaiians or other Pacific Islanders.	0	0	1 (2,9)	0	1 (1,4)
Not specified for patients due to data protection regulations	1 (9,1)	0	0	0	1 (1,4)
Ethnicity, n (%)[b]					
Hispanic or Latin American	9 (81,8)	20 (90,9)	32 (94,1)	6 (100,0)	67 (91,8)
Not Hispanic or Latino	2 (18,2)	2 (9,1)	2 (5,9)	0	6 (8,2)

Max, maximum; Min, minimum; SD, standard deviation

[a] Day 1 was the day of the first dose of vosoritide in either Study 111-206 (vosoritide/vosoritide participants) or Study 111-208 (placebo/vosoritide participants).

[b] Percentages were calculated using the total number of participants in the full analysis group (N for each treatment group) as the denominator.
Source: Interim CSR BMN 111-208, dated October 11, 2022; data cut date: January 26, 2022 Table 10.2.1.1 and Table 14.1.6.

	Age at day 1 of Vosoritid[a] (months)				
Feature	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6	Total N=73
Weight (kg)					
n	11	22	34	6	73
Mean (SD)	5,87 (0,60)	9,19 (0,89)	13,32 (2,38)	19,55 (6,23)	11,47 (4,36)

Feature	Age at day 1 of Vosoritid[a] (months)				
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6	Total N=73
Median	5,88	9,24	13,35	16,75	10,70
Min; Max	5,2; 6,9	7,0; 10,7	8,7; 19,1	14,8; 30,8	5,2; 30,8
Weight z-score[b]					
n	11	22	34	6	73
Mean (SD)	-1,67 (0,85)	-1,85 (0,73)	-1,34 (1,41)	-0,64 (1,94)	-1,49 (1,24)
Median	-1,49	-1,66	-0,89	-1,34	-1,53
Min; Max	-3,0; -0,4	-3,5; -0,7	-4,4; 0,9	-2,4; 2,4	-4,4; 2,4
BMI[c] ($kg/m2$)					
n	11	22	34	6	73
Mean (SD)	18,15 (1,36)	19,34 (1,41)	20,82 (2,15)	22,76 (4,69)	20,13 (2,46)
Median	18,12	19,48	20,77	20,60	19,84
Min; Max	16,3; 19,8	17,1; 21,6	15,5; 26,1	18,7; 30,3	15,5; 30,3
BMI z score[b,d]					
n	0	0	34	6	40
Mean (SD)	NA	NA	2,62 (0,95)	2,38 (0,66)	2,58 (0,91)
Median	NA	NA	2,70	2,27	2,69
Min; Max	NA	NA	-0,6; 4,4	1,7; 3,4	-0,6; 4,4

BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.
[a] Day 1 was the day of the first dose of vosoritide in either Study 111-206 (vosoritide/vosoritide participants) or Study 111-208 (placebo/vosoritide participants).
[b] Z-scores were determined using age- and sex-specific reference data (means and SDs) for children of average stature according to the Centers for Disease Control and Prevention.
[c] For height used to calculate BMI, body length took precedence over standing height for participants aged < 24 months. In the first year of treatment, for participants aged < 24 months at baseline and ≥ 24 months at week 52, body length had priority throughout the year.
[d] BMI-Z scores were derived only for participants aged 24 months or older.
Source: Interim CSR BMN 111-208, dated October 11, 2022; data cut date: January 26, 2022 Table 10.2.2.1.1 and Table 14.1.7.1.

Appendix Table 26. Baseline growth measures of the 111-208 study population

Growth measurement (unit)	Age at day 1 of Vosoritid[a] (months)				
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6	Total N=73
AGV[b] (cm/year)					
n	11	22	34	6	73
Mean (SD)	22,03 (3,87)	10,61 (3,75)	5,49 (1,78)	4,80 (0,91)	9,47 (6,44)
Median	22,32	9,91	5,41	4,79	6,68
Min; Max	16,4; 30,2	3,9; 18,5	0,6; 10,5	3,8; 6,1	0,6; 30,2
Height z-score[c]					
n	11	22	34	6	73

Growth measurement (unit)	Age at day 1 of Vosoritid[a] (months) 0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6	Total N=73
Mean (SD)	-3,42 (0,99)	-3,63 (0,75)	-4,72 (1,04)	-4,71 (1,10)	-4,19 (1,10)
Median	-3,30	-3,73	-4,41	-4,90	-4,08
Min; Max	-5,7; -2,2	-4,8; -2,1	-6,8; -3,1	-5,9; -2,8	-6,8; -2,1
Headroom (cm)					
n	11	22	34	6	73
Mean (SD)	56,83 (2,03)	68,98 (4,08)	79,72 (4,87)	91,86 (4,65)	74,03 (10,61)
Median	56,53	68,43	78,38	90,17	75,00
Min; Max	54,5; 60,1	62,2; 79,2	69,6; 89,3	88,7; 100,9	54,5; 100,9
Upper to lower body segment ratio					
n	11	22	34	6	73
Mean (SD)	3,03 (0,45)	2,62 (0,24)	2,31 (0,22)	2,11 (0,18)	2,49 (0,38)
Median	3,07	2,59	2,32	2,15	2,45
Min; Max	2,5; 4,0	2,3; 3,1	1,7; 2,7	1,9; 2,3	1,7; 4,0

AGV, annualized growth velocity; max, maximum; min, minimum; plc, placebo; SD, standard deviation; vos, vosoritid.
[a] Day 1 was the day of the first dose of vosoritide in Study 111-206 (vosoritide/vosoritide participants) or Study 111-208 (placebo/vosoritide participants).
[b] For participants who were 0 to <6 months of age at the start of vosoritide treatment, baseline AGV is defined as [(height at baseline - last height measurement at least 3 months before day 1)/(date of baseline assessment - date of last height measurement at least 3 months before day 1)] x 365.25. For all other participants, height 6 months before day 1 of vosoritide treatment is used instead.
[c] Z-scores were derived from age- and sex-specific reference data (means and SDs) for children with average stature according to the Centers for Disease Control and Prevention.
[d] For participants < 24 months of age, body length and length between crown and rump took precedence over standing height and sitting height. In the first year of treatment, body length and length between crown and rump had priority throughout the year for participants who were < 24 months of age at baseline and ≥ 24 months of age at week 52.
Source: Interim CSR BMN 111-208, dated October 11, 2022; data cut date: January 26, 2022 Table 10.2.2.2.1 and Table 14.2.7.2.

Appendix Table 27. Baseline characteristics Day 1 of Active Study Drug 111-301, 111-302, placebo and vosoritide

Characteristics	111-301 (Full Analysis Set)		111-302 (Full Analysis Set)	
	Placebo (n= 61)	Vosoritide 15 µg/kg (n=60)	Placebo/vosoritide (n=61)	Vosoritide/vosoritide (n=58)
Age at day 1 (years), mean (SD)	9.06 (2.47)	8.35 (2.43)	10.07 (2.48)	8.26 (2.42)
Gender, n (%)				
Male	33 (54.1)	31 (51.7)	33 (54.1)	30 (51.7)

Characteristics	111-301 (Full Analysis Set)		111-302 (Full Analysis Set)	
	Placebo (n= 61)	Vosoritide 15 µg/kg (n=60)	Placebo/vosoritide (n=61)	Vosoritide/vosoritide (n=58)
Female	28 (45.9)	29 (48.3)	28 (45.9)	28 (48.3)
Race, n (%)a				
White	45 (75.0)	41 (67.2)	41 (67.2)	44 (75.9)
Asian	10 (16.7)	13 (21.3)	12 (19.7)	9 (15.5)
Black or African American	3 (5.0)	2 (3.3)	2 (3.3)	3 (5.2)
Multiple	2 (3.3)	5 (8.2)	-	-
Japanese	-	-	4 (6.6)	2 (3.4)
Other	-	-	8 (13.1)	7 (12.1)
Ethnicity, n (%)a				
Not Hispanic or Latino	59 (98.3)	55 (90.2)	54 (88.5)	57 (98.3)
Hispanic or Latino	1 (1.7)	6 (9.8)	7 (11.5)	1 (1.7)
Tanner Stage b, n (%)				
I	48 (78.7)	48 (80.0)	42 (68.9)	47 (81.0)
>I	13 (21.3)	12 (20.0)	18 (29.5)	11 (19.0)
Not Done			1 (1.6)	0
Annualized growth velocity (cm/year) mean (SD)	4.06 (1.20)	4.26 (1.53)	3. 77 (1.29)	4.26 (1.54)
Height Z-score, mean (SD)	−5.14 (1.07)	−5.13 (1.11)	-5.14 (1.09)	-5.09 (1.11)
Standing Height, cm, mean (SD)	102.94 (10.98)	100.20 (11.90)	106.87 (10.84)	100.10 (12.08)
Sitting Height, cm, mean (SD)	68.46 (6.29)	66.24 (6.17)	70.75 (6.10)	66.16 (6.26)
Upper to Lower Body Segment Ratio, mean (SD)	2.01 (0.21)	1.98 (0.20)	1.98 (0.18)	1.98 (0.20)

Source: BioMarin 2020, 111-301 Final Clinical Study Report [30]; BioMarin 2021, 111-302 interim Clinical Study Report [29]
SD, standard deviation.
[a] Percentages were calculated using the total number of subjects in the full analysis set (N for each treatment group) as the denominator.
[b] The Tanner Scale is used to measure the physical development in children, adolescents, and adults. It consists of five stages (I, >I), where lower stages represent earlier phases of physical development. Tanner Stage (I, > I) is determined using the genitalia and breast Tanner Stage for males and females respectively.
Z-Scores were derived using age-sex specific reference data (means and SDS) for average stature children per the Centers for Disease Control and Prevention.

Appendix Table 28. Baseline characteristics and growth measures of patients included the studies used in the comparative analysis

Characteristic Variable	Study 111-901	Study 111-501	Study 111-202	Study 111-205	Study 111-206		Study 111-301	Study 111-302
Baseline demographics								
Analysis population	FAS (N=363)	FAS (N=186)	Safety, (N=35)	FAS (N=30)	FAS (N=44)		FAS (N=121)	FAS (N=119)
					Sentinel (N=8)	Randomized (N=36)		
Age, years, mean (SD)	5.14 (3.32)	21.7 (17.3)	7.6 (1.68)	8.16 (1.57)	32.12 (19.68) (months)	35.68 (15.10) (months)	8.71 (2.47)	9.18 (2.60)
Gender, n (%)a								
Male	184 (50.7)	85 (45.7)	16 (45.7%)	13 (43.3)	7 (87.5)	18 (50.0)	64 (52.9)	63 (52.9)
Female	179 (49.3)	101 (54.3)	19 (54.3%)	17 (56.7)	1 (12.5)	18 (50.0)	57 (47.1)	56 (47.1)
Race, n (%)a								
White	272 (74.9)		24 (68.6%)	21 (70.0)	7 (87.5)	29 (80.6)	86 (71.1)	85 (71.4)
Asian	51 (14.0)		7 (20.0%)	6 (20.0)	0	5 (13.9)	23 (19.0)	21 (17.6)
Black or African American	14 (3.9)		2 (5.7%)	-			5 (4.1)	5 (4.2)
Native Hawaiian/Pacific Islander	2 (0.6)				0	1 (2.8)		
Multiple	-		-	-			7 (5.8)	8 (6.7)
Japanese	17 (4.7)		-	1 (3.3)			7 (5.8)	6 (5.0)
Other	34 (9.4)		2 (5.7%)	5 (16.7)	0	5 (13.9)	16 (13.2)	
Not provided	3 (0.8)			2 (6.7)				
Ethnicity, n, (%)a								
Not Hispanic or Latino	326 (89.8)		32 (91.4%)	28 (93.3)	8 (100.0)	32 (88.9)	114 (94.2)	111 (93.3)
Hispanic or Latino	30 (8.3)		2 (5.7%)	2 (6.7)	0	2 (5.6)	7 (5.8)	8 (6.7)
Not Reported	7 (1.9)		1 (2.9%)		0	2 (5.6)		
Growth measures at baseline								

Characteristic Variable	Study 111-901	Study 111-501	Study 111-202	Study 111-205	Study 111-206		Study 111-301	Study 111-302
Analysis population	FAS (N=363)		Efficacy (N=34)	FAS (N=30)	Sentinel (N=8)	Randomized (N=36)	FAS (N=121)	FAS (N=119)
Annualized growth velocity (cm/year), mean (SD)			-	3.75 (1.28)	9.07 (3.37)	6.54 (3.51)	4.16 (1.37)	4.01 (1.43)
Height Z-score mean (SD)	-4.63 (1.39)		-	−5.12 (1.00)	-4.61 (0.43)	-4.52 (1.07)	−5.13 (1.09)	-5.12 (1.09)
Standing Height, cm, mean (SD)			100.19 (7.60)	100.16 (8.03)	75.01 (9.43)	76.82 (8.03)	101.58 (11.48)	103.57 (11.91)
Sitting Height, cm			66.39 (3.99)	66.46 (4.18)	52.83 (5.06)	53.66 (4.75)	67.36 (6.30)	68.51 (6.57)
Upper to Lower Body Segment Ratio, mean (SD)	2.26 (0.60)		1.99 (0.19)	1.99 (0.19)	2.41 (0.33)	2.34 (0.24)	2.00 (0.20)	1.98 (0.19)

SD, standard deviation

[a] Percentages were calculated using the total number of patients in the full analysis set (N for each treatment group) as the denominator. Abbreviations; FAS: Full analysis set; SD: standard deviation.

Z-Scores were derived using age-sex specific reference data (means and SDS) for average stature children per the Centers for Disease Control and Prevention.

Sources: BioMarin Clinical study report; 111-901 [25], 111-501[29], 111-202 [31], 111-205 [115], 111-206 [29], 111-301 [30], 111-302 [115]

15.2 Comparability of patients across studies

No relevant differences. Data prospectively collected in 111-901 was comparable and consistent with published data by Merker (2018)[5].

15.3 Comparability of the study populations with Danish patients eligible for treatment

No relevant differences [19, 20].

16. Appendix D Efficacy results per study

16.1 Definition, validity and clinical relevance of included outcome measures

The efficacy parameters evaluated (Appendix Table 29) reflected the previous studies of approved growth products [154, 155].

Appendix Table 29 Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Mean annualized growth velocity (AGV) (cm/year)	Average yearly rate of standing height growth [115]	Has been used to support approval of therapies in paediatric growth conditions including ACH[191]	AGV is an objective, non-invasive, reproducible endpoint that allows a treatment effect to be detected in the prevalent population within a year of treatment[191] Key indicator of skeletal growth; well-documented over the paediatric age range; highly sensitive to factors that impact growth negatively or positively; and easily and objectively measurable in an accurate non-invasive manner.[1]
Mean Height Z-score	Standard deviation score to compare standing height to age-and sex-appropriate reference heights[27]; higher scores reflect improvement [36] Age-specific reference (equivalent to 0) for average stature children calculated using CDC or WHO[1]	Standing height was converted to an age-appropriate and sexappropriate Z-score by comparison with Centers for Disease Control and Prevention reference standards[127]	Z-score is a patient-relevant outcome and improvements in Z-score have been shown to correlate with QoL in individuals with ACH [115] Z-score is a less variable measure than growth velocity in younger children (<5 years) with ACH[5] and is therefore more useful for detecting differences in efficacy between treated and untreated populations
Change from baseline standing height (cm)	Quantify treatment benefit on growth over the long-term period.[1]		

Outcome measure	Definition	Validity	Clinical relevance
Near-final adult height	Standing height when patients show AGV <1.5 cm/year and growth plate fusion [115]	The ultimate endpoint for medicines used in childhood for improvement of growth is the final adult height.[1]	Final adult height is a patient-relevant endpoint that is correlated with QoL in individuals with ACH[12] Near-final adult height allows the durability of the treatment effect to be assessed[33]
Upper to lower body segment ratio	The ratio of sitting height to lower body length, to measure body proportion [115], an indicator of changes to body proportionality, whereby ratio falls to 1 by approximately 10 years of age in average stature children and never reaches 1 in untreated children with ACH		Impaired growth in the lower limbs causes the upper body of ACH patients to represent a greater proportion of total height than the lower body, which is demonstrated by an upper-to-lower body segment ratio that is greater than the typical value of 1.4 seen in average stature individuals [96]. Upper to lower body segment ratio provides an assessment of whether the treatment effect is occurring proportionally in both the spine and the lower limbs[27]
Functional Independence Measure for Children (WeeFIM)	The WeeFIM instrument measures functional performance across 3 domains from the parent/caregiver's perspective (self-care [score range 8 to 56], mobility [score range 8 to 35], and cognition [score range 8 to 35]) and provides a total score between 18 and 126.	The validity and reliability of the WeeFIM instrument is well recognized and studies [123, 192, 193]	The WeeFIM measures the impact of developmental strengths and difficulties on independence at home, in school, and in the community. Functional assessment provides families and clinicians with a common language for describing a child's strengths and limitations [123]
The Pediatric Quality of Life Inventory (PedsQL) 4.0-generic score scales	Median change from baseline to Week 52 for PedsQL score (caregiver and self-reported). PedsQL is a tool aimed at recognizing clinical outcomes, including pain intensity, health-related quality of life, impact of the health-related condition on the family, and parents' satisfaction with the treatment.	PedsQL has been shown to be a reliable and valid measure of HRQOL for pediatric chronic health conditions[194, 195] including ACH.[73]	Utilization of HRQOL measures is a well-established and frequently used outcome measure aiming at improving patient health and determine the value of healthcare services. For short statured youth, improvement in HRQOL in addition to increasing linear growth, is an important endpoint in the treatment of these patients [196, 197]

Outcome measure	Definition	Validity	Clinical relevance
The Quality of Life in Short Statured Youth (QoLISSY) questionnaire	A disease-specific patient-reported outcome tool, using a 5-point Likert scale, designed for short-stature youth (child self-report and parent report versions) consisting of questions across seven domains.	The instrument has shown satisfactory reliability, adequate validity and ability to detect change in self-reported HRQOL[197, 198].	As above

16.2 Results per study

16.2.1 Description of methods used for estimation

Appendix Table 30. Description of methods used for estimation in the studies

Outcome	Description of methods used for estimation
Anthropometric measures	Anthropometric measures (of body dimension, size, and shape) were collected at approximately the same time at each scheduled visit (± 2 hours from the time when the first measurement assessment was taken at Screening) by a study staff member. These measures included (but were not limited to): standing height, sitting height, total body length (eg, if < 2 years of age and unable to walk), weight, head circumference, upper and lower arm length, leg length, and arm span. Standardized measuring equipment and detailed measurement techniques were detailed in the Anthropometric Measurement Guidelines. Three measurements were taken at each time point for which the mean value was reported.
Annualized growth velocity (AGV)	AGV was derived from the height measurements of subjects. This parameter required two height assessments for each subject and is annualized to cm/year. AGV as well as other growth parameters evaluated in these studies reflect experience from previous studies of approved growth products. [154, 155]
Height Z-score	All age-appropriate physical measurements were collected at approximately the same time each visit (±2 hours). Each measurement was taken in triplicate. The measurement of standing height at each scheduled visit was converted to age-and sex-appropriate standard deviation score (SDS), also referred to as Z-score, by comparison with non ACH reference standards (Centers for Disease Control and Prevention reference standards[127].
Upper to lower body segment ratio	Upper to lower body segment ratio is based on either body length and crown to rump or standing and sitting height and calculated as the ratio between sitting height and standing height minus sitting height.

Outcome	Description of methods used for estimation
Standing height & Sitting height	Preferred sitting height measurement: crown to rump for ages <24 months (if not measured, sitting height) and sitting height for ages >= 24 months (if not measured, crown to rump). Preferred standing height measurement: body length for ages < 24 months (if not measured, standing height) and standing height for ages >= 24 months (if not measured, body length).
The Pediatric Quality of Life Inventory (PedsQLTM 4.0)	A generic tool to measure HRQoL in children and adolescents that has both child self-report and parent-report versions and consists of questions across 4 domains. All items are presented on a 5-point Likert scale (0 = Never; 1 = Almost Never; 2 = Sometimes; 3 = Often; 4 = Almost always) and item scores are linearly transformed to a 0 to 100 scale and reverse scored, with higher scores indicating better HRQoL.
The Quality of Life in Short Stature Youth (QoLISSY®)	QoLISSY questionnaire is a disease-specific patient-reported outcome tool designed for short-stature youth which has both child self-report and parent-report versions and consists of questions across 7 domains. The items are rated on a 5-point Likert scale (1-Not at all/Never; 2-Slightly/Seldom; 3-Moderately/Quite Often; 4-Very/Very Often; 5-Extremely/Always) and yield a summary score ranging from 0 to 100, with higher values indicating a better HRQoL.
Pediatric Functional Independence Measure II (WeeFIM®-II)	An assessment tool that measures functional performance across three domains (self-care, mobility and cognition)[78, 199] It is a clinician-reported outcome measure which requires input from the parent/caregiver's perspective. Scoringscale: performance of a child on each of the individual items within the WeeFIM is assigned to one of seven levels on an ordinal scale that represent the function from complete and modified inde.pendence (levels 7 and 6) without a helping person to modified and complete dependence (levels 5 to 1) with a helping person. Measured by domain and total score.

16.2.2 Study 111-301

Power calculation

With 55 patients planned in each of the two randomised groups, the power to detect a difference of 1.75 cm/year between the vosoritide group and the placebo group in change from baseline in annualised growth velocity at 12 months was approximately 90%. This assumed the pooled SD of the change from baseline in annualised growth velocity was 2.80 cm/year, using a two-sided, two-sample *t* test at the 0.05 significance level. The power calculation was based on data from Study 111-202 [200]. All analyses were done with SAS version 9.4, using the Proc MIXED procedure [128].

Statistical analyses

The overall type I family-wise error rate for testing the primary and key secondary efficacy endpoints using an analysis of covariance (ANCOVA) model was controlled at the two-sided 0.05 significance level using a three-step serial gatekeeping multiple comparisons procedure. Following these multiple comparisons procedure, advancement to the next step only occurred if the null hypotheses within a step and the previous step(s) were all rejected at the significance level of 0.05 in favour of vosoritide. If any null hypothesis within a step was not rejected or was rejected but not in favour of vosoritide, the hypothesis tests corresponding to all subsequent steps would not be considered confirmatory. All hypothesis tests were two-sided. The models which tested the treatment difference always included the following

baseline covariates: strata (male Tanner stage I, female Tanner stage I, male Tanner Stage >I, female Tanner Stage >I); age, annualised growth velocity and height Z score [128].

A multiple imputation procedure, PROC MI, was to be used for the primary endpoint analysis to account for missing data. However, if there was insufficient data to apply this procedure, then a pre-specified alternative approach would be used by applying the baseline annualised growth velocity to the last available height assessment. As there were only two patients with missing data, this imputation approach was therefore used for the primary endpoint analysis. The two patients in the vosoritide treatment arm without a standing height assessment at week 52 had their missing standing height at week 52 imputed by applying baseline annualised growth velocity to the last available height assessment. Subsequently, these imputed standing height values were used to calculate their annualised growth velocity and height Z score at Week 52 [128].

Six prespecified subgroup analyses were also performed on each of the primary, and two key secondary efficacy endpoints. Forest plots provide an overall summary for the primary and key secondary endpoints, and of each subgroup, showing the difference between the treatment group least-squares mean change from baseline and the 95% CI for the difference, at Week 52.

Appendix Table 31. Results of 111-301 (NCT03197766)

Outcome	Study Arm	N a	Results (CI)/(SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	P value [d]		
Mean AGV (cm/year) week 52	Vosoritide	60	5.61 (1.05)	1.67	1.29, 2.05	p< 0.0001	See Appendix Table 30. Description of methods used for estimation in the studies Baseline annualised growth velocity was calculated from standing height measured over the last 6 months of the run-in study. Post-baseline annualised growth velocity was calculated from standing height at 52 weeks, and then summarised by treatment	Supplementary Table S1 Savarirayan 2020 [22] BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	61	3.94 (1.07)					
Mean change in AGV week 52 (cm/year)	Vosoritide	60	1.35 (±1.71)	1.47	0.85, 2.09	p<0.0001		
	Placebo	61	-0.12 (±1.74)					
Least-squares mean change from baseline in AGV week 52	Vosoritide	60	1.71 (1.40–2.01)	1.57	1.22, 1.93	P<0.0001		Savarirayan 2020 [22] BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	61	0.13 (-0.18–0.45)					

Outcome	Study Arm	N a	Results (CI)/(SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	P value [d]		
Mean Z-score week 52	Vosoritide	60	-4.89 (1.09)	[redacted]	[redacted]	[redacted]	group. Change from baseline in annualised growth velocity was derived for each patient as the difference between the post-baseline and baseline annualised growth velocity. ANCOVA models were applied to determine the least squares mean change from baseline treatment difference at 52 weeks and 95% CIs. All models provide the treatment difference adjusted for the following baseline covariates: strata: (male Tanner stage I, female Tanner stage I, male Tanner stage >I, female Tanner Stage >I); age; annualised growth velocity; and height Z score. The absolute difference in effect is estimated using a two-sided t-test.	Supplementary Table S2 Savarirayan 2020 [22], BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	61	-5.14 (1.09)					
Mean change in Z-score week 52	Vosoritide	60	0.24 (0.32)	[redacted]	[redacted]	[redacted]		
	Placebo	61	0.00 (0.28)					
Least-squares mean change from baseline in height Z-score week 52	Vosoritide	60	0.27 (0.17–0.36)	0.28	0.17, 0.39	p<0.0001		Savarirayan 2020 [22]
	Placebo	61	-0.01 (-0.10–0.09)					
Mean change in standing height week 52 (cm)	Vosoritide	60	5.59 (±1.06)	[redacted]	[redacted]	[redacted]		Supplementary Table S4 Savarirayan 2020 [22], BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	61	3.39 (±1.08)					
Least-squares mean change from baseline in standing height week 52 (cm)	Vosoritide	60	5.86 (5.56, 6.17)	1.57	1.21, 1.93	P=0.0001		
	Placebo	61	4.29 (3.97, 4.61)					
Mean change in sitting height week 52 (cm)	Vosoritide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Table 14.2.5.3, BioMarin 2020, 111-301 Final Clinical Study Report [109], BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	[redacted]	[redacted]					
Least-squares mean change from baseline in sitting	Vosoritide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Table 10.4.3.2.1, BioMarin 2020, 111-
	Placebo	[redacted]	[redacted]					

Outcome	Study Arm	N a	Results (CI)/(SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	P value [d]		
height week 52 (cm)								301 Final Clinical Study Report [109]
Mean change in upper to lower body segment ratio week 52	Vosoritide	60	-0.03 (±0.11)	0.00	[redacted]	[redacted]		Supplementary Table S3 Savarirayan 2020 [22], BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	61	-0.03 (±0.09)					
Least-squares mean change from baseline in upper to lower body segment ratio week 52	Vosoritide	60	-0.03 (-0.06–0.00)	-0.01	-0.05, 0.02	P=0.5060		Savarirayan 2020 [22]
	Placebo	61	-0.02 (-0.05–0.01)					
Median (IQR) change from baseline to Week 52 in QoLISSY (caregiver reported), week 52	Vosoritide	57	1.22 (-3.82, 11.64)	[redacted]	[redacted]	[redacted]		Supplementary Table S7 Savarirayan 2020 [22], BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	60	-1.73 (-6.94, 7.29)					
Median (IQR) change from baseline to Week 52 in QoLISSY (self-reportedc), week 52	Vosoritide	26	0.69 (-4.17, 8.34)	[redacted]	[redacted]	[redacted]		
	Placebo	35	1.39 (-7.64, 9.38)					
	Vosoritide	56	-0.54 (-7.61, 7.62)	[redacted]	[redacted]	[redacted]		

Outcome	Study Arm	N a	Results (CI)/(SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference [b]	95% CI	P value [d]		
Median change from baseline to Week 52 in PedsQL (caregiver reported), week 52	Placebo	57	2.96 (-5.43, 9.78)					Supplementary Table S6 Savarirayan 2020 [22], BioMarin, Data on File, TLGs Study 111-301 [201]
Median change from baseline to Week 52 in PedsQL score (self-reportedc), week 52	Vosoritide	25	1.09 (-6.68, 8.70)	[redacted]	[redacted]	[redacted]		
	Placebo	33	0.00 (-10.87, 6.52)					
Mean (SD) change from baseline to Week 52 in WeeFIM, week 52	Vosoritide	54	2.31 (8.01)	[redacted]	[redacted]	[redacted]		Supplementary Table S8 Savarirayan 2020 [22], BioMarin, Data on File, TLGs Study 111-301 [201]
	Placebo	59	1.86 (10.03)					

Abbreviations: AGV: annualised growth velocity; CI: confidence interval; IQR: interquartile range; LS: least square; NR: not reported; PedsQL: Pediatric Quality of Life Inventory, SD: standard deviation; WeeFIM: Functional Independence Measure for Children.

Change from baseline is based on the patients with available measurements at both time points.

a Two patients in the vosoritide group discontinued from the study before Week 52. The values for these 2 patients were imputed for this analysis.

b Difference is 15 µg/kg vosoritide minus placebo.

c Patients aged 8 years and older

Appendix Table 32. Median change from baseline to Week 52 in PedsQL score in 111-301

Change from baseline to Week 52	Caregiver-reported		Self-reported*		Reference
	Placebo	Vosoritide 15 µg/kg	Placebo	Vosoritide 15 µg/kg	
Emotional functioning					Supplementary Table S6 Savarirayan 2020 [22]
n	57	56	33	24	
Median (IQR)	5.00 (-5.00, 10.00)	5.00 (-5.00, 15.00)	0.00 (-10.00, 15.00)	0.00 (-7.50, 15.00)	
Social functioning					
n	57	56	33	25	
Median (IQR)	5.00 (-10.00, 12.50)	0.00 (-10.00, 12.50)	-5.00 (-15.00, 5.00)	0.00 (-10.00, 10.00)	
School functioning					
n	57	56	33	25	
Median (IQR)	0.00 (-10.00, 10.,00)	0.00 (-15.00, 10.00)	0.00 (-10.00, 10.00)	0.00 (-10.00, 15.00)	
Psychosocial health summary score					
n	57	56	33	25	
Median (IQR)	3.33 (−6.67, 8.92)	1.67 (−6.66, 10.00)	-2.14 (−5.00, 4.76)	0.00 (−6.66, 6.66)	
Physical health summary score					
n	57	56	33	25	
Median (IQR)	0	0	0	0	

Change from baseline to Week 52	Caregiver-reported		Self-reported*		Reference
	Placebo	Vosoritide 15 µg/kg	Placebo	Vosoritide 15 µg/kg	
	(−6.25, 9.38)	(−9.38, 9.38)	(−12.50, 9.37)	(−9.38, 6.25)	
Total score					
n	57	56	33	25	
Median (IQR)	2.96 (-5.43, 9.78)	-0.54 (-7.61, 7.62)	0 (-10.87, 6.52)	1.09 (-6.68, 8.70)	

**Patients aged 8 years and older.*
Abbreviations: IQR: interquartile range; PedsQL: Pediatric Quality of Life Inventory; µg: micrograms.
Source: Source: BioMarin 2020, 111-301 Final Clinical Study Report [109]

Appendix Table 33. Median change from baseline to Week 52 in QoLISSY score in 111-301

Change from baseline to Week 52	Caregiver-reported		Self-reported*		Reference
	Placebo	Vosoritide 15 µg/kg	Placebo	Vosoritide 15 µg/kg	
Physical					Supplementary Table S7 Savarirayan 2020 [22]
n	60	57	37	27	
Median (IQR)	4.16 (-8.34, 12.50)	0.00 (-12.50, 12.50)	0.00 (-8.34, 12.50)	4.16 (-4.17, 20.83)	
Social					
n	60	57	37	26	
Median (IQR)	4.69	0.00	-3.13	0.00	

Change from baseline to Week 52	Caregiver-reported		Self-reported*		Reference
	Placebo	Vosoritide 15 µg/kg	Placebo	Vosoritide 15 µg/kg	
	(-9.38, 14.07)	(-9.37, 9.37)	(-12.50, 12.50)	(-9.37, 9.37)	
Emotional					
n	60	57	35	27	
Median (IQR)	0.00 (-6.25, 9.37)	0.00 (-9.37, 6.25)	0.00 (-9.38, 9.38)	0.00 (-12.50, 15.62)	
Coping					
n	59	54	36	27	
Median (IQR)	0.00 (-7.50, 7.50)	-2.50 (-7.50, 7.50)	-1.25 (-13.75, 11.25)	-2.50 (-17.50, 17.50)	
Belief					
n	59	56	33	27	
Median (IQR)	0.00 (-12.50, 6.25)	0.00 (-6.25, 9.38)	0.00 (-12.50, 12.50)	6.25 (-6.25, 25.00)	
Future					
n	58	55	NA	NA	
Median (IQR)	0.00 (-10.00, 5.00)	0.00 (-5.00, 10.00)	NA	NA	
Effects on parents					
n	59	57	N/A	N/A	
Median (IQR)	0.00 (-7.50, 15.00)	-2.50 (-10.00, 10.00)	N/A	N/A	

Change from baseline to Week 52	Caregiver-reported		Self-reported*		Reference
	Placebo	Vosoritide 15 µg/kg	Placebo	Vosoritide 15 µg/kg	
Total score					
n	60	57	35	26	
Median (IQR)	1.22	-1.73	1.39	0.69	
	(-3.82, 11.64)	(-6.94, 7.29)	(-7.64, 9.38)	(-4.17, 8.34)	

Patients aged 8 years and older.
Abbreviations: IQR: interquartile range; NA: not applicable.

Appendix Table 34. Mean change from baseline to Week 52 in WeeFIM score in 111-301

Change from baseline to Week 52,mean (SD)	Placebo (n=59)	Vosoritide 15 µg/kg (n=54)	Reference
Self-care	2.20 (5.01)	1.89 (5.46)	Supplementary Table S8 Savarirayan 2020 [22]
Mobility	0.36 (3.67)	0.83 (2.99)	
Cognition	-0.69 (4.10)	-0.41 (3.52)	
Total score	1.86 (10.03)	2.31 (8.01)	

Abbreviations: SD: standard deviation; WeeFIM: Functional Independence Measure for Children.

16.2.3 Study 111-302

The most recent Efficacy Update Report (data cut-off date of 25 February 2022) presents change from baseline in AGV, height Z-score (average stature reference), height Z-score (ACH reference), standing height, and upper to lower body ratio up to the data cut-off [111, 112].

The evaluation of efficacy over time was assessed in the Full Analysis Set (FAS) population. The FAS was defined according to the intention-to-treat principle and included all enrolled subjects with a signed informed consent for 111-302. The FAS was used to present the baseline characteristics and efficacy data.

Safety population: all patients in the FAS who received at least one dose of vosoritide in Study 111-302.

No formal sample size calculations were performed. The sample size in this study is based on patients who completed Study 111-301. All efficacy endpoints were summarised at scheduled visits using descriptive statistics. For descriptive summaries, missing data were not imputed.

Appendix Table 35. Summary of results study 111-302 (NCT03424018), change from baseline to week 130 in AGV, height-z score and upper to lower body segment ratio for vos/vos and plc/vos*

Outcome	Study Arm	N	Results (SD)	95% Confidence Limits	Description of methods used for estimation	References
Mean AGV week 130	Vos/vos	[redacted]	[redacted]	[redacted]	See Appendix Table 30. Description of methods used for estimation in the studies All growth parameters were summarized using descriptive statistics and presented by treatment group (plc/vos and vos/vos) and overall. Change from baseline (defined as the last assessment prior to first dose of vosoritide) were summarized in a similar manner, with the addition of 95% confidence limits for the mean. ANCOVA models including four covariates that adjusted for baseline differences between treatment groups [strata: (male Tanner stage I, female Tanner stage I, male Tanner stage >I, female Tanner Stage >I); age; annualised growth velocity; and height Z score] were used to determine the treatment difference between vos/vos and plc/vos.	Efficacy Update Report 111-302 - Data cut-off date 25 Febrary, 2022 [111]
	Plc/vos	[redacted]	[redacted]	[redacted]		
AGV change from baseline to week 130[1], mean (SD)	Vos/vos	[redacted]	[redacted]	[redacted]		
	Plc/vos	[redacted]	[redacted]	[redacted]		
Height Z-score change from baseline to week 130[1], mean (SD)	Vos/vos	[redacted]	[redacted]	[redacted]		
	Plc/vos	[redacted]	[redacted]	[redacted]		
Upper to lower body segment ratio, change from baseline to week 130[1], mean (SD)	Vos/vos	[redacted]	[redacted]	[redacted]		
	Plc/vos	[redacted]	[redacted]	[redacted]		

Abbreviations: AGV: annualized growth velocity; CI: confidence interval; NR: not reported; SD: standard deviation

**The analysis visits were aligned across the two studies 111-301 and 111-302, so that all data summaries represent the same time on active treatment. Baseline is defined as the last assessment prior to the first dose of vosoritide. Therefore, for vos/vos participants, their baseline assessment is the same as in 111-301. For plc/vos participants, their baseline assessment is immediately prior to 111-302. Patients in the plc/vos started treatment 52 weeks later than those in the vos/vos.*

[1] Change from baseline was based on the subjects with available measurements at both time points

Appendix Table 36. 111-302 (NCT03424018) Cumulative AGV over time*

Mean AGV (SD) (cm/year)	Plc/vos	Vos/vos	Overall	References
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	Efficacy Update Report 111-302 - Data cut-off date 25 Febrary, 2022 [111]
Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to Week 52, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 78, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to Week 78, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 104, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 104, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 130, mean (SD)	[redacted]	[redacted]	[redacted]	

Mean AGV (SD) (cm/year)	Plc/vos	Vos/vos	Overall	References
Change from baseline to week 130, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 156, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 156, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 182, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 182, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 208, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 208, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 234, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 234, mean (SD) [1]	[redacted]	[redacted]	[redacted]	

Mean AGV (SD) (cm/year)	Plc/vos	Vos/vos	Overall	References
Week 260, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 260, mean (SD) [1]	[redacted]	[redacted]	[redacted]	

Abbreviations: AGV: annualized growth velocity; NA: Not applicable; SD: standard deviation
[1]Change from baseline is based on the participants with available measurements at both time points
**The analysis visits were aligned across the two studies 111-301 and 111-302, so that all data summaries represent the same time on active treatment. Baseline is defined as the last assessment prior to the first dose of vosoritide. Therefore, for vos/vos participants, their baseline assessment is the same as in 111-301. For plc/vos participants, their baseline assessment is immediately prior to 111-302. Patients in the plc/vos started treatment 52 weeks later than those in the vos/vos.*
AGV at each 12-month interval is derived over the previous 12-months. For example, Month 24 Interval = [(Height at Month 24 Visit- Height at Month 12 Visit)/(Date of Month 24 Visit - Date of Month 12 Visit)] x 365.25.

Appendix Table 37. 111-302 (NCT03424018) height Z-score over time*

Mean AGV (SD) (cm/year)	Plc/vos	Vos/vos	Overall	References
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	Efficacy Update Report 111-302 - Data cut-off date 25 Febrary, 2022 [111]
Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to Week 52, mean (SD)[1]	[redacted]	[redacted]	[redacted]	
Week 78, mean (SD)	[redacted]	[redacted]	[redacted]	

Mean AGV (SD) (cm/year)	Plc/vos	Vos/vos	Overall	References
	[redacted]	[redacted]	[redacted]	
Change from baseline to Week 78, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 104, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 104, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 130, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 130, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 156, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 156, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 182, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 182, mean (SD) [1]	[redacted]	[redacted]	[redacted]	

Mean AGV (SD) (cm/year)	Plc/vos	Vos/vos	Overall	References
	[redacted]	[redacted]	[redacted]	
Week 208, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 208, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 234, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 234, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 260, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 260, mean (SD) [1]	[redacted]	[redacted]	[redacted]	

Abbreviations: SD: standard deviation, NA: Not Applicable

[*]The analysis visits were aligned across the two studies 111-301 and 111-302, so that all data summaries represent the same time on active treatment. Baseline is defined as the last assessment prior to the first dose of vosoritide. Therefore, for vos/vos participants, their baseline assessment is the same as in 111-301. For plc/vos participants, their baseline assessment is immediately prior to 111-302. Patients in the plc/vos started treatment 52 weeks later than those in the vos/vos.

[1]Change from baseline is based on the participants with available measurements at both time points.

Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

Appendix Table 38. Upper to lower body segment ratio over time*

Mean upper to lower body segment ratio	Plc/vos	Vos/vos	Overall	References
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	Efficacy Update Report 111-302 - Data cut-off date 25 Febrary, 2022 [111]
Week 52, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to Week 52, mean (SD)[1]	[redacted]	[redacted]	[redacted]	
Week 78, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 78, mean (SD)[1]	[redacted]	[redacted]	[redacted]	
Week 104, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 104, mean (SD)[1]	[redacted]	[redacted]	[redacted]	
Week 130, mean (SD)	[redacted]	[redacted]	[redacted]	

Mean upper to lower body segment ratio	Plc/vos	Vos/vos	Overall	References
Change from baseline to week 130, mean (SD)[1]	[redacted]	[redacted]	[redacted]	
Week 156, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 156, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 182, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 182, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 208, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 208, mean (SD) [1]	[redacted]	[redacted]	[redacted]	
Week 234, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 234, mean (SD) [1]	[redacted]	[redacted]	[redacted]	

Mean upper to lower body segment ratio	Plc/vos	Vos/vos	Overall	References
Week 260, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline to week 260, mean (SD) [1]	[redacted]	[redacted]	[redacted]	

Abbreviations: SD: standard deviation, NA: Not Applicable

[*]The analysis visits were aligned across the two studies 111-301 and 111-302, so that all data summaries represent the same time on active treatment. Baseline is defined as the last assessment prior to the first dose of vosoritide. Therefore, for vos/vos participants, their baseline assessment is the same as in 111-301. For plc/vos participants, their baseline assessment is immediately prior to 111-302. Patients in the plc/vos started treatment 52 weeks later than those in the vos/vos.

[1]Change from baseline is based on the participants with available measurements at both time points. Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

Appendix Table 39. 111-302, Completer analysis showing Analysis of Covariance for Upper to Lower Body Segment Ratio at Baseline and at 24 months

Upper to Lower Body Segment Ratio	111-901/301 Placebo (N=38)	111-301/302 15 µg/kg BMN 111 (N=45)	Reference
Baseline			
n	38	45	Table S1, Savarirayan R., et al., Genetics in Medicine, August 2021 [96]
Mean (SD)	2.00 (0.16)	1.97 (0.20)	
Median	2.01	2.01	
25th, 75th Percentile	1.91, 2.12	1.89, 2.10	
Min, Max	1.5, 2.4	1.3, 2.2	
Month 24			
n	38	45	

Upper to Lower Body Segment Ratio	111-901/301 Placebo (N=38)	111-301/302 15 µg/kg BMN 111 (N=45)	Reference
Mean (SD)	1.95 (0.15)	1.88 (0.21)	Table S1, Savarirayan R., et al., Genetics in Medicine, August 2021 [96]
Median	1.96	1.88	
25th, 75th Percentile	1.88, 2.07	1.79, 2.01	
Min, Max	1.6, 2.2	1.3, 2.3	
Change from baseline			
n	38	45	Table S1, Savarirayan R., et al., Genetics in Medicine, August 2021 [96]
Mean (SD)	-0.05 (0.09)	-0.09 (0.11)	
Median	-0.04	-0.10	
25th, 75th Percentile	-0.08, 0.01	-0.17, -0.02	
Min, Max	-0.4, 0.1	-0.3, 0.1	
LS mean change from baseline (95% CI)	-0.02 (-0.07, 0.02)	-0.07 (-0.11, -0.04)	
Difference in LS mean change from baseline (95% CI)		-0.05 (-0.09, -0.01)	

Abbreviations: CI: confidence interval; LS: least square: SD: standard deviation
For description of methods used for estimation See Appendix Table 30. Description of methods used for estimation in the studies

16.2.4 Study 111-202

The following populations were defined for the initial 6-month period and the extension period. The number of patients in each population was summarised by cohort in the initial 6-month period and by dose level in the extension period.

Enrolled Population: all patients who consented and were screened and eligible.

Safety Analysis Population: all patients who received at least one dose of study treatment and were used for safety analysis in the initial 6-month period and entire study period.

Extension Safety Analysis Population: all patients who received at least one dose of study treatment in the extension period and were used for safety analysis in the extension period.

Efficacy Analysis Population: for the initial 6-month period and the extension period, all patients who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population, respectively.

Pharmacokinetic (PK) Analysis Population: for the initial 6-month period and the extension period, all patients who received at least one dose of study treatment in this study and had any post-treatment PK information in the corresponding period.

Thirty-five patients with ACH participated in this study; no formal sample size calculations were performed. Patients who discontinued prematurely after Day 10 were not replaced. Missing dates or partially missing dates were imputed conservatively for concomitant medications and AEs to ensure that an AE was considered treatment emergent and had the longest possible duration.

Appendix Table 40. Results of 111-202 (NCT02055157) and 111-205 (NCT02724228) treatment duration up to 42 months

Outcome	Study Arm	N	Results mean (SD) [95% CI]	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value		
Mean change from baseline to 48 months in AGV (cm/year)	Cohort 1 Vosoritide 2.5 µg/kg	8	[redacted]	NA	NA	[redacted]	All growth parameters were measured three times for each assessment and summarized using descriptive statistics. Baseline AGV was established based on the results of the observational study 111-901, based on standing height measurements during the 6 months prior to the baseline in study 111-202. AGV (cm/year) at a Post-baseline Visit was defined as ([Height at Post-baseline Visit -	BioMarin Interim CSR 111-205 [115], Table 10.4.1.1.1
	Cohort 2 Vosoritide 7.5 µg/kg	8	[redacted]	NA	NA	[redacted]		
	Cohort 3 Vosoritide 15 µg/kg	10	[redacted]	NA	NA	[redacted]		
	Cohort 4 Vosoritide 30 µg/kg	9	[redacted]	NA	NA	[redacted]		

Outcome	Study Arm	N	Results mean (SD) [95% CI]	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value		
			[redacted]			[redacted]	Height at Screening]/[Date of Post-baseline Visit - Date of Screening Assessment]) x 365.25. Testing for the hypothesis of no variation from baseline of AGV was performed using a paired t-test. The p-value was considered descriptive.	
Mean Z-score change from BL in standing height, 48 months	Cohort 1 Vosoritide 2.5 µg/kg	6	[redacted]	NA	NA	[redacted]	See Appendix Table 30. Description of methods used for estimation in the studies. Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention. Testing for the hypothesis of no variation from baseline of Z-score was performed using a paired t-test.	BioMarin Interim CSR 111-205 [115], Table 10.4.1.2.1
	Cohort 2 Vosoritide 7.5 µg/kg	6	[redacted]	NA	NA	[redacted]		
	Cohort 3 Vosoritide 15 µg/kg	9	[redacted]	NA	NA	[redacted]		
	Cohort 4 Vosoritide 30 µg/kg	8	[redacted]	NA	NA	[redacted]		
Mean change from BL in upper to lower body	Cohort 1 Vosoritide 2.5 µg/kg	6	[redacted]	NA	NA	[redacted]	The variation in body proportion ratios compared to baseline at each scheduled assessment	BioMarin Interim CSR 111-205 [115], Table 14.2.3.1

Outcome	Study Arm	N	Results mean (SD) [95% CI]	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value		
segment ratio, 48 months	Cohort 2 Vosoritide 7.5 µg/kg	6	[redacted]	NA	NA	[redacted]	point was presented at 6 months. Testing for the hypothesis of no variation from baseline was performed using a two-sided paired t-test.	
	Cohort 3 Vosoritide 15 µg/kg	9	[redacted]	NA	NA	[redacted]		
	Cohort 4 Vosoritide 30 µg/kg	8	[redacted]	NA	NA	[redacted]		

Abbreviations; BL: baseline; NA: Not applicable; NR: Not reported;

Appendix Table 41. Results of 111-202 (NCT02055157) AGV over time by Cohort

	Mean (SD) AGV (cm/year)				Description of methods used for estimation	References
	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)		
Baseline	3.90 (1.11)	2.89 (1.39)	4.04 (2.28)	4.39 (1.15)	See Appendix Table 30. Description of methods used for estimation in the studies Change from Baseline was calculated as the difference between current value and baseline.	Savarirayan et al. 2019. [27] BioMarin 2018(A) Clinical Study Report: 111-202.[31]
Month 6	3.38 (0.89)	4.17 (1.28)	6.06 (1.07)	6.58 (1.18)		
Change from baseline to Month 6; (SD) 95% CI	-0.37 (1.59); -1.84, 1.10	1.28 (1.44); 0.07, 2.48	2.01 (2.00); 0.58, 3.44	2.08 (2.14); 0.30, 3.87		
Month 12	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) AGV (cm/year)				Description of methods used for estimation	References
	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)		
Change from baseline to Month 12; (SD) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]		
Month 18	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline to Month 18; (SD) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]		
Month 24	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline to Month 24; (SD) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]		

Appendix Table 42. Results of 111-202 (NCT02055157) Height Z-score over time by Cohort

	Mean (SD) height Z-score					Description of methods used for estimation	References
	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)	All Cohorts (n=35)		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Appendix Table 30. Description of methods used for estimation in the studies.	BioMarin 2018(A) Clinical Study Report: 111-202.[31]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) height Z-score					Description of methods used for estimation	References
	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)	All Cohorts (n=35)		
Change from baseline to Month 6; (SD) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Change from Baseline was calculated as the difference between current value and baseline.	
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline to Month 12; (SD) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline to Month 18; (SD) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline to Month 24; (SD) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: CI: confidence interval; N/A: not applicable; SD: standard deviation.

16.2.5 Study 111-205

FAS: was defined according to the intention-to-treat principle and includes all enrolled participants. The FAS was used to present the baseline characteristics and efficacy data. Efficacy summaries include assessments up to the cut-off date, or 45 days post treatment discontinuation.

Safety Population: all patients in the FAS who receive at least one dose of the study drug in Study 111-205.

PK Population: all patients in the Safety Population who have at least one evaluable PK concentration in Study 111-205.

Immunogenicity Population: all patients in the Safety Population who have at least one evaluable immunogenicity sample in Study 111-205.

All efficacy endpoints were assessed on the FAS population by the cohort into which they were enrolled into in Study 111-202 and overall. No formal sample size calculations were performed. Missing data were not imputed other than for partial/missing dates.

Appendix Table 43. 12-month interval AGV over time, Study 111-205

	Mean (SD) AGV (cm/year)					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Appendix Table 30. Description of methods used for estimation in the studies Change from Baseline was calculated as the difference between current value and baseline.	BioMarin, Efficacy update report 111-205, 2023 [117]
Month 12 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 12 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 24 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 24 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 36 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) AGV (cm/year)					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 36 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 48 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 48 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 60 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 60 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 72 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 72 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) AGV (cm/year)					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
Month 84 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 84 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 96 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 96 interval, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

AGV, annualized growth velocity; SD, standard deviation. Baseline AGV was established using Study 111-901 data in the 6 months prior to the screening visit in Study 111-202. [a]Change from baseline is based on the participants with available measurements at both time points. AGV at each visit is derived over the previous 12-month period. For example, AGV Month 12 interval = [(Standing height at Month 12 Visit - Standing height at Screening Visit) / (Date of Month 12 Visit - Date at Screening Visit)] x 365.25.

Appendix Table 44. Height z-score over time

	Mean (SD) height z-score, SDS					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Appendix Table 30. Description of methods used for estimation in the studies Change from Baseline was calculated as the difference between current value and baseline.	*BioMarin, Efficacy update report 111-205, 2023 [117]*
Month 12, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 12, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 36, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 36, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) height z-score, SDS					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
Month 48, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 48, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 60, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 60, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 72, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 72, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 84, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 84, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) height z-score, SDS					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 96, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 96, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations; SD: standard deviation

Baseline is the last available assessment before the first dose of study drug in Study 111-202.

[a]Change from baseline is based on the participants with available measurements at both time points. Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

Appendix Table 45. Upper to lower body segment ratio over time

	Mean (SD) height z-score, SDS					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See Appendix Table 30. Description of methods used for estimation in the studies	*BioMarin, Efficacy update*

	Mean (SD) height z-score, SDS					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
Month 12, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Change from Baseline was calculated as the difference between current value and baseline.	*report 111-205, 2023 [117]*
Change from baseline[a] to Month 12, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 24, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 36, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 36, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 48, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 48, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) height z-score, SDS					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 60, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 60, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 72, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 72, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 84, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Change from baseline[a] to Month 84, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Month 96, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

	Mean (SD) height z-score, SDS					Description of methods used for estimation	References
	Cohort 1 2.5 ug/kg (N=6)	Cohort 2 7.5 ug/kg (N=6)	Cohort 3 15 ug/kg (N=10)	Cohort 4 30 ug/kg (N=8)	Overall (N=30)		
Change from baseline[a] to Month 96, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: SD: Standard deviation
Baseline is the last available assessment before the first dose of study drug in Study 111-202. a Change from baseline is based on the participants with available measurements at both time points.

16.2.6 Study 111-206

Analyses

Determination of sample size

No formal sample size calculations were performed. Approximately 70 patients aged 0 to <60 months at study entry were planned for participation and this sample size was considered appropriate to evaluate the efficacy and safety of vosoritide in the target population.

Analysis populations

The FAS was defined according to the intent-to-treat principle and included all enrolled sentinel and randomised patients.

The FAS (randomised) was a subset of the FAS and was considered the primary analysis population for the assessment of the efficacy parameters of height Z-score, height, AGV and upper to lower body segment ratio.

All safety analyses were based on the Safety Population, which includes all sentinel and randomised patients in the FAS who received at least one dose of vosoritide or placebo in this study [119].

Adjustments for covariates

The efficacy analyses used an ANCOVA model including adjustments for the following baseline covariates: randomisation age stratum, age at baseline, baseline AGV, and sex. Analyses of height Z-score, standing height, and upper to lower body ratio included their baseline as an additional covariate [119].

Handling of dropouts or missing data

For descriptive summaries, missing data were not imputed. For model-based analyses, if the required assessment at Week 52 was missing but there were assessments before and after Week 52, a linear interpolation using the measurements closest to the before and after Week 52 were used. Otherwise, for those with no assessment after Week 52, multiple imputation by using placebo data from patients in the same cohort was used to impute the missing values for height and upper to lower body segment ratio at Week 52. Other than for partial/missing dates, there was no imputation for safety data [119].

Examination of subgroups

Model-based analyses in the FAS population were conducted by cohort, and summary tables were presented by stratified age within Cohort 1 (≥24 months to <36 months and ≥36 months to <60 months) and Cohort 2 (≥6 months to <15 months and ≥15 months to <24 months) [119].

Appendix Table 46. Results of 111-206 (NCT03583697) change from baseline to week 52 in AGV, Z-score, standing height and upper to lower body segment ratio

Outcome Cohort 1, FAS randomized subjects	Study Arm	N	Results (SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference [a]	95% CI [a]	P value [b]		
Mean (SD) AGV (cm/year) at baseline	Vosoritide	15	[redacted]	[redacted]				
	Placebo	16	[redacted]					
Mean (SD) AGV (cm/year) at week 52	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]	See Appendix Table 30. Description of methods used for estimation in the studies The absolute difference in effect is estimated using a two-sided t-test.	BioMarin, Data on File, TLGs Study 111-206 Anthro Measures [202]
	Placebo	16	[redacted]					
Mean (SD) change from baseline to week 52 in AGV (cm/year)	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) Z-score at baseline	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		

Outcome Cohort 1, FAS randomized subjects	Study Arm	N	Results (SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference [a]	95% CI [a]	P value [b]		
Mean (SD) Z-score at week 52	Placebo	16	[redacted]					
Mean change from baseline to week 52 in Z-score	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) standing height at baseline (cm)	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) standing height at week 52	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) change from baseline to week 52 in standing height (cm)	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) upper to lower body segment ration, at baseline	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) upper to lower body segment ratio at week 52	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) change from baseline to week 52 in upper	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					

Outcome Cohort 1, FAS randomized subjects	Study Arm	N	Results (SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference [a]	95% CI [a]	P value [b]		
to lower body segment ratio								

Abbreviations: Annualised growth velocity: AGV; SD: standard deviation.
**Change from baseline was based on the subjects with available measurements at both time points*
.[a]Difference is vosoritide minus placebo
[b]Two-sided p-value

Appendix Table 47. Results HRQoL 111-206 change from baseline to week 52

Outcome Cohort 1, FAS	Study Arm	N	Results (SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference[a]	95% CI	P value [b]		
Mean (SD) ITQoL Overall Health score, at baseline	Vosoritide	19	[redacted]	[redacted]	[redacted]	[redacted]		BioMarin, Data on File, TLGs Study 111-206 QoL measures [203]
	Placebo	14	[redacted]					
Mean (SD) ITQoL Overall Health score, at week 52	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	14	[redacted]					
Mean (SD) change from baseline to week 52 in ITQoL Overall Health *	Vosoritide	15	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	12	[redacted]					

Outcome Cohort 1, FAS	Study Arm	N	Results (SD)	Estimated absolute difference in effect			Description of methods used for estimation	References
				Difference[a]	95% CI	P value [b]		
Mean (SD) WeeFIM total score, at baseline	Vosoritide	19	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	14	[redacted]					
Mean (SD) WeeFIM total score, at at week 52	Vosoritide	19	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	16	[redacted]					
Mean (SD) change from baseline to week 52 in WeeFIM total score*	Vosoritide	19	[redacted]	[redacted]	[redacted]	[redacted]		
		14	[redacted]					

Abbreviations: ITQoL: infant toddler Quality of life questionnaire; SD: standard deviation; WeeFIM: Functional Independence Measure for Children

**Change from baseline was based on the subjects with available measurements at both time points*

[a]*Difference is vosoritide minus placebo*

[b]*Two-sided p-value*

16.2.7 Study 111-208

Appendix Table 48. Results on Annual growth velocity at 6-months interval over time - all treated patients - Study 111-208

Study BMN 111-208	Age at day 1 of Vosoritid (months)			
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

Study BMN 111-208	Age at day 1 of Vosoritid (months)							
	0 to <6 N=11		≥6 to <24 N=22		≥24 to <60* N=34		≥60* N=6	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Month 6								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Change compared to baseline until month 6[a]								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Month 12								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Change compared to baseline until month 12[a]								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Month 18								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	

Study BMN 111-208	Age at day 1 of Vosoritid (months)							
	0 to <6 N=11		≥6 to <24 N=22		≥24 to <60* N=34		≥60* N=6	
Change compared to baseline until month 18[a]								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Month 24								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Change compared to baseline until month 24[a]								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Month 30								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Change compared to baseline until month 30[a]								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Month 36								

Study BMN 111-208	Age at day 1 of Vosoritid (months)							
	0 to <6 N=11		≥6 to <24 N=22		≥24 to <60* N=34		≥60* N=6	
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Change compared to baseline until month 36[a]								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Month 42								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	
Change compared to baseline until month 42[a]								
n	[redacted]		[redacted]		[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
25th; 75th percentile	[redacted]		[redacted]		[redacted]		[redacted]	
Min; Max	[redacted]		[redacted]		[redacted]		[redacted]	

AGV, annualized growth velocity; NA, not applicable; SD, standard deviation.

aChange from baseline was based on subjects with available measurements at both time points. Baseline was defined as the last examination before starting the active study drug.

** Only the age group ≥24 to <60 months and the age group ≥60 months are relevant for the indication to be evaluated (achondroplasia ≥2 years). Age group ≥6 to <24 months and age group 0 to <6 months are outside the indication. For subjects who were 0 to <6 months of age at the start of treatment with vosoritide, baseline AGV is defined as [(size at baseline - last size measurement at least 3 months before day 1)/(date of baseline measurement - date of last size measurement at least 3 months prior to day 1)] x 365.25. For all other subjects, the*

Height used 6 months prior to day 1 of vosoritide treatment. AGV is administered at each visit via the previous 6-month period derived. For example: AGV week 26 to week 52 = [(size at visit in week 52 - size at visit in week 26)/(date of visit in week 52 - date of visit in week 26)] x 365,25. For subjects <24 months of age, body length takes precedence over standing height. In the first year of treatment For subjects <24 months of age at baseline and ≥24 months of age at week 52, body length is the priority throughout the year.
Source: Interim CSR BMN 111-208, dated October 11, 2022; data cut January 26, 2022; Table 10.4.2.2.1 and Table 14.2.2.2.3. [32].

Appendix Table 49. Results height z-score over time after first dose of vosoritide

Height z-score	Age at day 1 of Vosoritid (months)			
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 26				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change compared to baseline until week 26[a]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				

Height z-score	Age at day 1 of Vosoritid (months)			
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change compared to baseline until week 52[a]				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 78				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change compared to baseline until week 78[a]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]

Height z-score	Age at day 1 of Vosoritid (months)			
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change compared to baseline until week 104[a]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 130				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change compared to baseline until week 130[a]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 156				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Height z-score	Age at day 1 of Vosoritid (months)			
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60* N=34	≥60* N=6
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change compared to baseline until week 156[a]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 182				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Change compared to baseline until week 182[a]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
25th; 75th percentile	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]

FAS, complete analysis set; NA, not applicable; SD, standard deviation.

a Change from baseline was based on subjects with available measurements at both time points. Baseline was defined as the last examination before starting the active study drug.

** Only the age group ≥24 to <60 months and the age group ≥60 months are relevant for the indication to be evaluated (achondroplasia ≥2 years). Age group ≥6 to <24 months and age group 0 to <6 months are outside the indication.*

Height z-score	Age at day 1 of Vosoritid (months)			
	0 to <6	≥6 to <24	≥24 to <60*	≥60*
	N=11	N=22	N=34	N=6

Z-scores for height were determined using age- and sex-specific reference data (means and SDs) for children with average height according to the Centers for Disease Control and Prevention (CDC). For participants aged <24 months, body length took precedence over standing height. In the first year of treatment, for participants aged < 24 months at baseline and ≥ 24 months at week 52, body length had priority throughout the year.
Source: Interim CSR BMN 111-208, dated October 11, 2022; data cut January 26, 2022; Table 10.4.1.1.1, Table 14.2.1.1.3. [32].

Appendix Table 50. Upper to Lower body segment ration over time - All treated

Upper to Lower Body Segment Ratio	Age on Day 1 of Vosoritide (Months)			
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60 N=34	≥60 N=6
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline to Week 52[a]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline to Week 78[a]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Upper to Lower Body Segment Ratio	Age on Day 1 of Vosoritide (Months)			
	0 to <6 N=11	≥6 to <24 N=22	≥24 to <60 N=34	≥60 N=6
Mean change from baseline to Week 104[a]	[redacted]	[redacted]	[redacted]	[redacted]
Week 130				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline to Week 130[a]	[redacted]	[redacted]	[redacted]	[redacted]
Week 156				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline to Week 156[a]	[redacted]	[redacted]	[redacted]	[redacted]
Week 182				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline to Week 182[a]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Change from baseline was based on the participants with available measurements at both time points. Baseline was defined as the last assessment prior to initiation of the active study drug.

Subjects aged < 24 months, body length and crown to rump length take precedence over standing height and sitting height. For the first year of treatment, subjects aged < 24 months at baseline and ≥ 24 months at Week 52, body length and crown to rump length take precedence throughout the year.

Source: Interim CSR BMN 111-208, dated October 11, 2022; data cut January 26, 2022; Table 14.2.2.3.3 [32].

16.2.8 Study 111-901

Appendix Table 51. Results of 111-901 Comparison of length/height by age and sex in children with achondroplasia in the present study and other studies

Age	Mean height cm (SD) Female			Mean height cm (SD) Male			References
	Study 111-901	Published study (Hoover-Fong 2017)	Published study (Merker 2018)	Study 111-901	Published study (Hoover-Fong 2017)	Published study (Merker 2018)	
N	21	34	155	26	37	133	Savarirayan, R., 2022. [98], Hoover-Fong 2008 [35], Merker 2018 [5]
1 Year	65.78 (2.75)	63.9 (2.6)	64.6 (2.4)	67.06 (3.04)	64.9 (2.3)	65.9 (2.2)	
N	24	30	93	26	41	92	
2 years	72.65 (3.28)	70.4 (2.8)	71.5 (2.7)	73.30 (2.91)	71.8 (2.6)	72.9 (2.4)	
N	55	32	122	54	34	83	
5 years	86.93 (3.89)	85.2 (3.7)	85.7 (3.9)	87.69 (3.57)	86.1 (3.5)	87.2 (3.1)	
N	38	13	67	28	12	55	
10 years	105.72 (7.09)	105.0 (6.0)	105.7 (5.0)	108.31 (7.50)	104.9 (5.8)	106.2 (4.4)	
N	3	6	49	9	5	30	
13 years	118.23 (11.07)	113.0 (7.2)	116.7 (5.3)	118.71 (6.68)	116.3(6.9)	117.0 (4.9)	

Appendix Table 52. 111-901 (NCT01603095) Median AGV for patients in 111-901 compared with average stature children

Age	111-901 population (N=342) median AGV (IQR), cm/year	Average stature population (N=202) median AGV, cm/year	Description of methods used for estimation	References
<1 year*	[redacted]	44	See Appendix Table 30. Description of methods used for estimation in the studies	BioMarin 111-901 Clinical Study Report [25]. Hoover-Fong 2008 [35]
1–<2 years*	[redacted]	14.4		
2–10 years*	[redacted]	5.5 – 7		

**Not specifically defined in average stature population.*
Abbreviations: AGV: annualised growth velocity; IQR: inter-quartile range.

Appendix Table 53. 111-901 Summary of results: Mean height Z-score (Using CDC Reference For All Ages), mean Upper to Lower Body Segment ratio by Age at the Time of Assessment, PedsQL, QoLISSY and WeeFIM; mean total score self-reported and caregiver reported. Analysis Population: Full Analysis Set, Excluding Any Assessments On Or After Limb Lengthening, Growth Therapies or Investigational Drug:

Age	(N=363) Height Z-score, mean (SD)	(N=363) Upper to lower body segment ratio, mean (SD)	(N=363) PedsQL, total score mean (SD)		(N=363) QoLISSY, total score mean (SD)		(N=363) WeeFIM®, total score mean (SD)	References
			Self-reported	Caregiver-reported	Self-reported	Caregiver-reported		
<1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Age	(N=363) Height Z-score, mean (SD)	(N=363) Upper to lower body segment ratio, mean (SD)	(N=363) PedsQL, total score mean (SD)		(N=363) QoLISSY, total score mean (SD)		(N=363) WeeFIM®, total score mean (SD)	References
			Self-reported	Caregiver-reported	Self-reported	Caregiver-reported		
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	BioMarin 111-901 Clinical Study Report [25].
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
9 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
12 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
13 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Age	(N=363) Height Z-score, mean (SD)	(N=363) Upper to lower body segment ratio, mean (SD)	(N=363) PedsQL, total score mean (SD)		(N=363) QoLISSY, total score mean (SD)		(N=363) WeeFIM®, total score mean (SD)	References
			Self-reported	Caregiver-reported	Self-reported	Caregiver-reported		
14 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

For description of methods used for estimation See Appendix Table 30. Description of methods used for estimation in the studies

16.2.9 Study 111-501

Appendix Table 54. Results of 111-501 (NCT03449368), final standing height

Age at assessment (n)	Final standing height (cm)	Description of methods used for estimation	References
3-4 years (n=1)	[redacted]	Final standing height is most recent height measurement within 1 year of study enrolment. For children (i.e., subjects ≤16 years of age), final standing height (in centimeters) was defined as the most recently recorded standing height measurement within one year of study enrolment and data collection (i.e., the index date). Accordingly, children without a height measurement within one year of the index date were excluded from the analyses. For adults (i.e., subjects >16 years of age), final standing height was based on the most recently recorded standing height	Additional table 1: BioMarin 2020, 111-501 Observational Study Report [9]
5-8 years (n=50)	[redacted]		
9-10 years (n=17))	[redacted]		
11-13 years (n=17)	[redacted]		
14-15 years (n=17)	[redacted]		
16-18 years (n=13)	[redacted]		
19-20 years (n=5)	[redacted]		
>20 years (n=66)	[redacted]		

Age at assessment (n)	Final standing height (cm)	Description of methods used for estimation	References
		measurement in relation to the index date (made when subjects were >16 years of age). Accordingly, adults without a height measurement made after 16 years of age at any time (not limited to the five-year follow-up) during the historical follow-up were excluded from all analyses.	

Appendix Table 55. Results of 111-501 (NCT03449368), quality of life

Questionnaire	Children	Parents	Overall	References
QoLISSY Questionnaire Total score, mean (SD)	63.4 (22.2) N=65	54.8 (21.0) N=106	58.0 (21.8) N=171	Table 35: BioMarin 2020, 111-501 Observational Study Report [9]; Maghnie, 2023 [97]
PedsQL Questionnaire, total score, mean (SD)	69.3 (16.3) N=105	67.6 (16.8) N=97	NR	Table 37: BioMarin 2020, 111-501 Observational Study Report [9] Maghnie, 2023 [97]
WeeFIM Questionnaire, total score, mean (SD)	-	-	112.7 (13.3) N=98	Table 39: BioMarin 2020, 111-501 Observational Study Report [9] Maghnie, 2023 [97]

For description of methods used for estimation See Appendix Table 30. Description of methods used for estimation in the studies

Correlation coefficients for associations between clinical characteristics and measures of quality of life were estimated as specified in the table below (Appendix Table 56). Missing values were managed through pairwise deletion, where all available observations were used to calculate each pairwise correlation without regard to whether variables outside that pair were missing. In other words, coefficients were estimated based on available observations for each pairwise correlation, as opposed to available observations across all variables. For analyses of instrument outcomes, only subjects with total scores were included, but missing domain scores were allowed. [204]

Appendix Table 56. Type of correlations for Association Analysis by Variable Type

Variable type	Continuous	Ordinal	Dichotomous
Continuous	Pearson's (r)	Spearman's (p)	Point-biserial (r_{pb})
Ordinal	Spearman's (p)	-	Rank-biserial (r_{pb})
Dichotomous	Point-biserial (r_{pb})	Rank-biserial (r_{pb})	Pearson's (r)

Appendix Table 57. Correlation coefficient between clinical characteristics and PedsQL score

PedsQL domain (n=61)	Correlation coefficient between clinical characteristic and PedsQL score (Pearson's coefficients)		Description of methods used for estimation	References
	Height	Height Z-score		
Physical score	0.041	0.273**	Coefficients were estimated based on available observations for each pairwise correlation, as opposed to available observations across all variables. For analyses of instrument outcomes, only subjects with total scores were included, but missing domain scores were allowed. There are no general criteria for how to interpret correlation coefficients. However, the following absolute cut-off values can serve as a starting point for further interpretation and contextualization: • 0.9 to 1.0 – Very high correlation;	Maghnie et al. 2021 [204]
Social score	0.200	0.177		
Emotional score	0.054	0.100		
School score	-0.054	0.255**		
Psychosocial score	0.076	0.218*		
Total score	0.068	0.266**		

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PedsQL domain (n=61)	Correlation coefficient between clinical characteristic and PedsQL score (Pearson's coefficients)		Description of methods used for estimation	References
	Height	Height Z-score		
			• 0.7 to <0.9 – High correlation; • 0.5 to <0.7 – Moderate correlation; • 0.3 to <0.5 – Low correlation; and • 0.0 to <0.3 – Negligible correlation.	

**p<0.1; **p<0.05.*
Abbreviations: PedsQL: Pediatric Quality of Life Inventory.

Appendix Table 58. Correlation coefficient between clinical characteristics and QoLISSY score

QoLISSY domain (n=64)	Correlation coefficient between clinical characteristic and QoLISSY score (Pearson's coefficients)		Description of methods used for estimation	References
	Height	Height Z-score		
Physical score	0.387***	0.466***	As described in Appendix Table 57	Maghnie et al. 2021 [204]
Social score	0.366***	0.345***		
Emotional score	0.203*	0.229*		
Coping score	0.052	−0.230*		
Beliefs score	0.159	0.324***		
Future score	0.117	0.268**		
Effects score	0.232*	0.059		

Total score	0.361***	0.394***

*p<0.1; **p<0.05; ***p<0.01.
Abbreviations: QoLISSY: Quality of Life in Short Stature Youth.

Appendix Table 59. Correlation coefficient between clinical characteristics and WeeFIM score

WeeFIM domain (n=55)	Correlation coefficient between clinical characteristic and WeeFIM score (Pearson's coefficients)		Description of methods used for estimation	References
	Height	Height Z-score		
Self-care score	0.423***	0.339***	As described in Appendix Table 57	Maghnie et al. 2021 [204]
Mobility score	0.399***	0.404***		
Cognition score	0.076	0.036		
Total score	0.407***	0.351***		

*p<0.1; **p<0.05; ***p<0.01.
Abbreviations: WeeFIM: paediatric functional independence measure.

17. Appendix E Safety data for intervention and comparator(s)

17.1 Safety data overall summary

Appendix Table 60. Overall Summary of Adverse Events for all safety populations

AE Category	Pure 15 µg/kg (N=131)	Maximum 15 µg/kg (N=148)	All Treated (N=164)
Subjects with any AE, n (%)[a]	**102 (77.9)**	**119 (80.4)**	**135 (82.3)**
AEs leading to dose reduction	0	0	0
AEs leading to dose interruption	22 (16.8)	29 (19.6)	33 (20.1)
AEs leading to study drug discontinuation	2 (1.5)	2 (1.4)	3 (1.8)
AEs leading to study discontinuation	0	0	0
AEs leading to study drug or study discontinuation	2 (1.5)	2 (1.4)	3 (1.8)
Subjects with any SAE, n (%)[a]	**6 (4.6)**	**8 (5.4)**	**9 (5.5)**
SAEs leading to dose reduction	0	0	0
SAEs leading to dose interruption	4 (3.1)	5 (3.4)	6 (3.7)
SAEs leading to study drug discontinuation	0	0	0
SAEs leading to study discontinuation	0	0	0

AE, adverse event; EOI, event of interest; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; N: total number of subjects in treatment group; n, number of subjects with event; NCI, National Cancer Institute; SAE, serious adverse event.

AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version 22.0 and graded for severity using NCI CTCAE version 4.0.

a Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects with more than one AE of the same category were counted only once for that category.

b Relationship to study drug was assessed by the Investigator.

Source: EPAR [126]

Appendix Table 61. Adverse Events by CTCAE Grade – Pooled Safety Population

CTCAE Grade	Pure 15 µg/kg (N=131; treatment exposure=149.86 PY)		Maximum 15 µg/kg (N=148 treatment exposure=217.88 PY)		All Treated (N=164 treatment exposure=255.13 PY)	
	Incidence n (%) [a]	Event Rate m (rate) [b]	Incidence n (%) [a]	Event Rate m (rate) [b]	Incidence n (%) [a]	Event Rate m (rate) [b]
Subjects with any AE, n (%)	102 (77.9)	10345 (69.03)	119 (80.4)	15293 (70.19)	135 (82.3)	20158 (79.01)
Grade 1	93 (71.0)	10175 (67.90)	110 (74.3)	14968 (68.70)	125 (76.2)	19791 (77.57)
Grade 2	47 (35.9)	132 (0.88)	61 (41.2)	257 (1.18)	68 (41.5)	279 (1.09)
Grade 3	5 (3.8)	7 (0.05)	9 (6.1)	11 (0.05)	10 (6.1)	12 (0.05)
Grade > 3	0	-	0	-	0	-
Missing	12 (9.2)	31 (0.21)	18 (12.2)	57 (0.26)	23 (14.0)	76 (0.30)

AE, adverse event; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; m, number of events; N, total number of subjects in treatment group; n, number of subjects with event; NCI, National Cancer Institute; PT, preferred term; PY, person-years; SOC, system organ class.

AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version 22.0 and graded for severity using NCI CTCAE version 4.0.

a Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects with more than one AE of the same SOC/PT/CTCAE grade were counted only once for that SOC/PT/CTCAE grade.

b Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure in each treatment group. Multiple occurrences of an AE with the same SOC/PT/CTCAE grade for a subject were counted for each occurrence for that SOC/PT/CTCAE grade.

Source: EPAR [126]

Appendix Table 62. Overall Summary of Adverse Events –comparison to Placebo from trial 111-301

	Placebo	15 µg/kg Vosoritide
Subjects with any AE, n (%)a	**60 (98.4)**	**59 (98.3)**
AEs leading to dose reduction	0	0
AEs leading to dose interruption	10 (16.4)	10 (16.7)
AEs leading to study drug discontinuation	0	1 (1.7)
AEs leading to study discontinuation	0	0
AEs leading to study drug or study discontinuation	0	1 (1.7)
Subjects with any SAE, n (%)a	**4 (6.6)**	**3 (5.0)**
SAEs leading to dose reduction	0	0
SAEs leading to dose interruption	2 (3.3)	2 (3.3)
SAEs leading to study drug discontinuation	0	0
SAEs leading to study discontinuation	0	0
SAEs leading to study drug or study discontinuation	0	0
Subjects with any treatment-related AE, n (%)[a,b]	**51 (83.6)**	**53 (88.3)**
Treatment-related SAEs	0	0
Subjects with any AE of CTCAE grade ≥ 3, n (%)[a]	**3 (4.9)**	**3 (5.0)**
Subjects who died, n (%)[a]	**0**	**0**
Subjects with any EOI, n (%)[a]		
Injection site reactions	50 (82.0)	51 (85.0)

	Placebo	15 µg/kg Vosoritide
Blood pressure decreases	3 (4.9)	8 (13.3)
Heart rate change	0	0
Hypersensitivity (SMQ Narrow Terms)	7 (11.5)	16 (26.7)
Avascular necrosis or osteonecrosis	0	0

AE, adverse event; EOI, event of interest; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; N: total number of subjects in treatment group; n, number of subjects with event; NCI, National Cancer Institute; SAE, serious adverse event.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version 22.0 and graded for severity using NCI CTCAE version 4.0.
a Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects with more than one AE of the same category were counted only once for that category.
b Relationship to study drug was assessed by the Investigator.
Source: EPAR [126]

Appendix Table 63. Adverse Events by CTCAE Grade – 111-301 (Safety Population)

CTCAE Grade	Placebo (N=61; treatment exposure=60.93 PY)		15 µg/kg Vosoritide (N=60; treatment exposure=57.99 PY)	
	Incidence n (%)a	Event Rate m (rate)b	Incidence n (%)a	Event Rate m (rate)b
Subjects with any AE, n (%)	60 (98.4)	2121 (34.8)	59 (98.3)	7345 (126.7)
Grade 1	59 (96.7)	2059 (33.8)	58 (96.7)	7294 (125.8)
Grade 2	24 (39.3)	57 (0.9)	19 (31.7)	46 (0.8)
Grade 3	3 (4.9)	5 (0.1)	3 (5.0)	5 (0.1)
Grade > 3	0	0	0	0

AE, adverse event; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; m, number of events; N, total number of subjects in treatment group; n, number of subjects with event; NCI, National Cancer Institute; PT, preferred term; PY, person-years; SOC, system organ class.
AEs with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. AEs were coded using MedDRA version 22.0 and graded for severity using NCI CTCAE version 4.0.
a Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects with more than one AE of the same SOC/PT/CTCAE grade were counted only once for that SOC/PT/CTCAE grade.
b Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure in each treatment group. Multiple occurrences of an AE with the same SOC/PT/CTCAE grade for a subject were counted for each occurrence for that SOC/PT/CTCAE grade.
Source: EPAR [126]

17.2 Safety data per study

17.2.1 Study 111-301 and 111-302

Safety analyses study 111-301

All randomised and consented patients, constituting the full analysis set, were included according to intention-to-treat principles for the efficacy analyses (n=121). All patients who received at least one dose of vosoritide or placebo (n=121) were included in the safety analyses. The safety population was defined as all patients in the full analysis set who

received at least one dose of vosoritide or placebo. Safety was assessed by examining the incidence, severity, and relationship to study drug of all treatment-emergent adverse events was reported during the study period. In addition, changes from baseline in clinical laboratory results and vital signs were assessed. Summary tables by treatment group included all safety events up to 30 days following treatment discontinuation [128].

Appendix Table 64. Summary of patients experiencing adverse events during treatment in 111-301

AE category, n (%)*	Placebo (n=61)	Vosoritide 15 µg/kg (n=60)
Patients with any TEAE	60 (98.4)	59 (98.3)
AEs leading to dose reduction	0	0
AEs leading to dose interruption	10 (16.4)	10 (16.7)
AEs leading to trial drug discontinuation	0	1 (1.7)
AEs leading to trial discontinuation	0	0
AEs leading to trial drug or trial discontinuation	0	1 (1.7)
Patients with any SAE	4 (6.6)	3 (5.0)
SAEs leading to dose reduction	0	0
SAEs leading to dose interruption	2 (3.3)	2 (3.3)
SAEs leading to trial drug discontinuation	0	0
SAEs leading to trial discontinuation	0	0
SAEs leading to trial drug or trial discontinuation	0	0
Patients with any TRAE**	51 (83.6)	53 (88.3)
TRSAEs	0	0
Patients with any AE of NCI CTCAE Grade ≥3	3 (4.9)	3 (5.0)
Patients who died	0	0
Injection site reactions	29 (47.5)	44 (73.3)
Blood pressure decrease***	3 (4.9)	7 (11.7)
Heart rate change	0	0
Hypersensitivity (SMQ Narrow Terms)	7 (11.5)	16 (26.7)
Avascular necrosis or osteonecrosis	0	0
Slipped capital femoral epiphysis	0	0
Fractures	0	1 (1.7)

**Percentages were calculated using the total number of patients in the safety population (N for each treatment group) as the denominator. Patients with more than one AE of the same category were counted only once for that category.*
***Relationship to trial drug was assessed by the investigator.*
****MedDRA preferred terms included for blood pressure decreases: blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure orthostatic decreased, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, diastolic hypotension, hypotension, and orthostatic hypotension.*
Abbreviations: AE: adverse event; EOI: event of interest; CTCAE: common terminology criteria for adverse events; NCI: National Cancer Institute; SAE: serious adverse event; SMQ: Standardised MedDRA Query Analysis; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event; TRSAE: treatment-related serious adverse events.
Source: Savarirayan (2020) [22]

Appendix Table 65. Overall incidence of adverse events among the safety population in 111-302 (31st October 2019 data cut)

AE category	PLC/VOS (n=61)*	VOS/VOS (n=58)**	Overall (N=119)
Patients with any AE, n (%)***	[redacted]	[redacted]	[redacted]
AEs leading to dose reduction	[redacted]	[redacted]	[redacted]
AEs leading to dose interruption	[redacted]	[redacted]	[redacted]
AEs leading to trial drug discontinuation	[redacted]	[redacted]	[redacted]
AEs leading to trial discontinuation	[redacted]	[redacted]	[redacted]
AEs leading to trial drug or trial discontinuation	[redacted]	[redacted]	[redacted]
Patients with any SAE, n (%)***	[redacted]	[redacted]	[redacted]
SAEs leading to dose reduction	[redacted]	[redacted]	[redacted]
SAEs leading to dose interruption	[redacted]	[redacted]	[redacted]
SAEs leading to trial drug discontinuation	[redacted]	[redacted]	[redacted]
SAEs leading to trial discontinuation	[redacted]	[redacted]	[redacted]
SAEs leading to trial drug or trial discontinuation	[redacted]	[redacted]	[redacted]
Patients with any TRAE, n (%)***,‡	[redacted]	[redacted]	[redacted]
TRSAEs	[redacted]	[redacted]	[redacted]
Patients with any AE of NCI CTCAE Grade ≥3, n (%)***	[redacted]	[redacted]	[redacted]
Patients who died, n (%)	[redacted]	[redacted]	[redacted]
Injection site reactions	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]
Heart rate change	[redacted]	[redacted]	[redacted]
Hypersensitivity (SMQ Narrow Terms)	[redacted]	[redacted]	[redacted]
Avascular necrosis or osteonecrosis	[redacted]	[redacted]	[redacted]
Slipped capital femoral epiphysis	[redacted]	[redacted]	[redacted]
Fractures	[redacted]	[redacted]	[redacted]

**Received placebo in 111-301 followed by 15 µg/kg vosoritide daily in 111-302.*

***Received 15 µg/kg vosoritide daily in 111-301 and continued this treatment in 111-302.*

****Percentages were calculated using the total number of patients in the safety population (N for each treatment group) as the denominator. Patients with more than one AE of the same category were counted only once for that category.*

‡Relationship to trial drug was assessed by the investigator.

Abbreviations: AE: adverse event; CTCAE: common terminology criteria for adverse events; NCI: National Cancer Institute; SAE: serious adverse event; SMQ: Standardised MedDRA Query Analysis; TRAE: treatment-related adverse event; TRSAE: treatment-related serious adverse events.

Source: BioMarin 2020, Interim Clinical Study Report: 111-302 [33]

Appendix Table 66. Safety summary 111-302 (plc/vos and vos/vos) (25th February, 2022 data cut)

Event	Overall (N=119)*
Patients with any AE, n (%)***	116 (97,5)
AEs leading to trial drug discontinuation	0
AEs leading to trial discontinuation	0
AEs leading to trial drug or trial discontinuation	0
Patients with any SAE, n (%)	14 (11.8)
Patients with any TRAEs, n (%)	36 (30.3)
TRSAEs	1 (0.8)
Patients with any AE of NCI CTCAE Grade ≥3, n (%)	12 (10.1)
Patients who died, n (%)	0
Injection site reactions CTCAE grade ≥2	2(1.7)
Avascular necrosis or osteonecrosis	0
Slipped capital femoral epiphysis	0
Fractures	5 (4.2)

Abbreviations: AE: adverse event; CTCAE: common terminology criteria for adverse events; NCI: National Cancer Institute; SAE: serious adverse event; TRAE: treatment-related adverse event; TRSAE: treatment-related serious adverse events.
**Includes plc/vos patients who received placebo in 111-301 followed by 15 µg/kg vosoritide daily in 111-302 and vos/vos patients who received 15 µg/kg vosoritide daily in 111-301 and continued this treatment in 111-302.*
Source: Hoover-Fong et al., 2023 [112]

17.2.2 Study 111-202 and 111-205

Appendix Table 67. Summary of adverse events experienced by patients over the entire study period by Cohort in 111-202

Adverse event category, n (%)	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)	All Cohorts (N=35)
Patients with any TEAE (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs related to trial drug*(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with any SAE (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs related to trial drug* (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to trial drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event category, n (%)	Cohort 1 (n=8)	Cohort 2 (n=8)	Cohort 3 (n=10)	Cohort 4 (n=9)	All Cohorts (N=35)
discontinuation (%)					
TEAE leading to trial discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**Relationship to trial drug was assessed by the investigator.*
***7-year-old male with non-serious grade 1 intermittent Wolff Parkinson-White syndrome, discovered during routine per-protocol ECG monitoring. The patient had no clinical symptoms associated with this finding and remained asymptomatic and without reported supraventricular tachycardia for the duration of his participation in the study. After the patient discontinued study drug after the last dose on 24 September 2015, the patient's parents made the decision to withdraw from the study.*
Abbreviations: ECG: electrocardiogram; TEAE, treatment-emergent adverse event; SAE, serious adverse event.
TEAE is any AE that newly appeared or worsened in severity following the initiation of study drug.
Source: Table 12.2.1.2: BioMarin 2018, Clinical Study Report: 111-202 [31]

Appendix Table 68. Summary of adverse events experienced by patients over the entire study period by Cohort in 111-205

Adverse event category, n (%)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=10)	Cohort 4 (n=8)	Overall (N=30)
Patients with any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with any SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with any treatment-related* AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with any AE of NCI CTCAE Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**Relationship to trial drug was assessed by the investigator.*
Abbreviations: AE: adverse event; CTCAE: common terminology criteria for adverse events; NCI: National Cancer Institute; SAE: serious adverse event.
TEAE is any AE that newly appeared or worsened in severity following the initiation of study drug.
Source: BioMarin 2020, Interim Clinical Study Report: 111-205 [115]

17.2.3 Study 111-206

Appendix Table 69. Summary of adverse events experienced by patients over the entire study period by Cohort in 111-206

AE category, n (%)*	Cohort 1 (Sentinel) (n=4) (Age ≥24 to <60 months)		Cohort 2 (Sentinel) (n=4) (Age ≥6 to <24 months)		Overall (N=8)	
	Sentinel (n=4)	Randomised (n=26)	Sentinel (n=4)	Randomised (n=10)	Sentinel (N=8)	Randomised (N=36)
Patients with any AE	[redacted]					
AEs leading to dose interruption	[redacted]					
Patients with any SAE	[redacted]					
Patients with any treatment-related** AE, n (%)	[redacted]					
Patients with any AE of NCI CTCAE Grade ≥3	[redacted]					
Deaths	[redacted]					

**Percentages were calculated using the total number of patients in the safety population (N for each treatment group) as the denominator. Patients with more than one AE of the same category were counted only once for that category.*

***Relationship to trial drug was assessed by the investigator.*

Abbreviations: AE: adverse event; CTCAE: common terminology criteria for adverse events; NCI: National Cancer Institute; SAE: serious adverse event.

Source: BioMarin 2020, Interim Clinical Study Report: 111-206 and 111-208 [29]

17.2.4 Study 111-208

Appendix Table 70. Results for Adverse Events of 111-208, by severity (NCI CTCAE Grades 1-5) -Safety population

Study BMN 111-208	Age at day 1 of Vosoritid (months)									
	0 to <6 N=11		≥6 to <24 N=22		≥24 to <60* N=34		≥60* N=6		Total (N=73)	
NCI CTCAE Grade	Incidence n (%) [a]	Event rate m (rate) [b]	Incidence n (%) [a]	Event rate m (rate)[b]	Incidence n (%) [a]	Event rate m (rate) [b]	Incidence n (%) [a]	Event rate m (rate)[b]	Incidence n (%) [a]	Event rate m (rate)[b]
Total treatment exposure (person-years)	[redacted]									
Subjects with one AE	[redacted]									

Grade 1	[redacted]									
Grade 2	[redacted]									
Grade 3	[redacted]									
Missing	[redacted]									
Degree ≥3	[redacted]									

AE, Adverse Event; m, total number of events; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with the event; SOC, system organ class.
Drug-related AEs that occurred or worsened after initiation of treatment with the active study drug and up to 30 days after the last dose of study drug were included. AEs were coded using MedDRA version 24.1 and graded by severity using NCI CTCAE version 4.03.
[a] Percentages were calculated using the total number of participants in the safety population (N for each treatment group) as the denominator. Participants with more than one drug-related AE of the same SOC/PT/CTCAE grade were counted only once for that SOC/PT/CTCAE grade.
[b] Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure in each treatment group. Multiple occurrences of a drug-related AE with the same SOC/PT/CTCAE grade in a participant were counted for each occurrence for that SOC/PT/CTCAE grade.
**Only the age group ≥24 to <60 months and the age group ≥60 months are relevant for the indication to be evaluated (achondroplasia ≥2 years). Age group ≥6 to <24 months and age group 0 to <6 months are outside the indication.*
Source: Interim CSR BMN 111-208, dated October 11, 2022; data cut date: January 26, 2022 Table 11.2.3.4.1. [32].

17.2.5 Study 111-901

Appendix Table 71. Overview of Incidence of Adverse Events: Full Analysis Set in 111-901

AE category	Overall (N=363)
Subjects with any AE, n (%)	[redacted]
AEs leading to study discontinuation	[redacted]
Subjects with any SAE, n (%)	[redacted]
SAEs leading to study discontinuation	[redacted]
Subjects with any AE of CTCAE grade >3, n(%)[a]	[redacted]
Subjects who died, n (%)	[redacted]

AE, adverse event; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; SAE, serious adverse event.
AEs with onset or worsening after the start of the study were included. AEs were coded using MeDRA version 23.0 and graded for severity using NCI CTCAE version 4.0.
a Percentages were calculated using the total number of subjects as the denominator. Subjects with more than on AE of the same category were conducted only once for that category.
Source: BioMarin Clinical Study Report 111-901 [25]

17.2.6 Study 111-501

No safety data collection and individual case processing will be implemented for this study. This epidemiological, non-interventional study does not solicit any safety data collection and reporting from subjects or Investigators, nor intend to collect and prospectively follow-up information about the use of a specific medicinal product and potential related safety concerns. The Investigator-reported data is based on secondary use of data already collected for another purpose (study is based on data abstraction from healthcare records).

18. Appendix F Comparative analysis of efficacy and safety

18.1 Statistical Methods for Comparative Analyses

18.1.1 Comparative analysis population

The comparative analyses included comparisons between the vosoritide group (consisting of several treatment groups from studies 111-202/205 and 111-301) and the external control group (untreated ACH subjects from the NH sources). The subjects included in the external control group were selected by a sex and age matching process to each subject in the vosoritide group. Sex and age are the most critical factors when tracking the development of skeletal growth as evidenced by CDC growth charts as well as published height data in the ACH population, which are all summarized by sex and age (CDC 2019, Hoover-Fong 2008, Hoover-Fong 2017, Merker 2018, Del Pino 2019).

The external control group included the subset of subjects from the NH data source who had a confirmed diagnosis of ACH, available sex data, and at least one standing height assessment available that was taken at a known age. Post-event height assessments were excluded for those subjects who received vosoritide or growth hormone, or underwent limb lengthening surgery. Each subject was matched by sex and age to the vosoritide subject. If subjects had height assessments at different ages, this primary step resulted in subjects from the NH source being matched to more than one subject in the vosoritide group. When this occurred, subjects from the NH source were randomly assigned to one sex and age group of the vosoritide subjects, with an equal probability. Similarly, if multiple subjects in the vosoritide group had the same sex and age, the same set of subjects from the NH source were matched to all of the vosoritide subjects. When this occurred, the subjects from the NH source were assigned to one of the vosoritide subjects, with equal probability. The matching algorithm resulted in each subject in the vosoritide group being matched to a unique group of subjects from the NH sources with a different number of NH subjects in each matched group. [33]

18.1.2 Primary Analysis

5-Year Cross-Sectional Comparative Analysis (TTest)

To adjust for baseline height differences, the primary cross-sectional analysis method subtracted the difference at baseline between the height of each vosoritide subject and the mean height of their matched external control from the height difference at Year 5 between the height of each vosoritide subject and the mean height of their matched external control using the corresponding analysis population at Year 5 (i.e., Month 60). Similarly, the difference was calculated at Baseline using the corresponding analysis population at the baseline. The difference between the difference of height at Year 5 and that at Baseline was calculated and tested by using one sample t-test. SAS Proc TTest was used to estimate the mean difference between the difference of active arm versus control arm at Year 5 and that at Baseline with 2-sided p-value and 95% confidence interval (CI). [33]

Appendix Figure 2. Illustration of Primary 5-Year Cross Sectional Analysis

Legend: yellow circle, vosoritide treated subject; grey circles, matched NH controls; Δ, difference between the estimate for a vosoritide treated subject and the mean of the estimates among its age- and gender-matched NH control subjects.
Source: BioMarin (2020) Natural History Integrated Analyses Report, Figure 3.2.1 [33]

18.1.3 Supportive Analyses

5-Year Cross-Sectional Comparative Analysis (ANCOVA)

The comparative analyses included comparisons between the vosoritide group (Cohort 3 [15 µg/kg] of 111-202/205) and the sex and age matched external control group (untreated ACH subjects from the NH sources). Cross-sectional analyses at Year 5 and Baseline used an ANCOVA model that included the fixed-effects of treatment (active arm vs. NH arm) and indicator variables for the matching based on sex and age combination. SAS Proc Mixed was used to estimate the least square (LS) mean difference between the active arm versus control arm with 2-sided p-value and 95% CI**.** In addition, sensitivity and supportive analyses were performed to assess the robustness of the results. [33]

18.2 Results of Comparative Analyses

The results of the pre-specified primary analysis (based on Cohort 3 [15 µg/kg dose] of 111-202/111-205) are summarised in Appendix Table 72 (based on Cohort 3 [15 µg/kg dose] of 111-202/111-205).

Appendix Table 72. Height difference at Year 5 and baseline (cross-sectional)

	Primary analysis	Supportive pooled analysis		
	Vosoritide 15 µg/kg	External control (primary)	Vosoritide 15 µg/kg	External control (supportive)
Height (cm) at Year 5				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Means difference (95% CI)	[redacted]		[redacted]	
Two-sided p value	[redacted]		[redacted]	
Height (cm) at baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Means difference (95% CI)	[redacted]		[redacted]	
Two-sided p value	[redacted]		[redacted]	
Height (cm) difference (Year 5 – baseline)				
Means (95% CI)	[redacted]		[redacted]	
Two-sided p value	[redacted]		[redacted]	

Abbreviations: CI: confidence interval; max: maximum; min: minimum; SD: standard deviation. Source: BioMarin 2020, Natural history integrated analyses report [33]

5-Year Longitudinal Comparative Analyses (Cohort 3 of 111-202/205) on Height

An ANCOVA model, with fixed effects for treatment and indicator variables for matching factors of sex and age, was applied for the 5-year longitudinal analyses to compare the change in height from baseline at Year 5 between the 10 subjects from Cohort 3 of 111-202/205 to sex and age matched subjects from the Primary NH Descriptive Population with 5 years follow-up.

Appendix Table 73. Longitudinal Analysis of Covariance of Change from Baseline in Height for Cohort 3 of 111-202/205 (Analysis Population: 5-Year Longitudinal Comparative Analysis versus Primary External Control)

Change from Baseline in Height at Year 5	External Control (Primary) (N = 98)	Vosoritide 15 µg/kg (N = 10)
Mean (SD)	[redacted]	[redacted]
LS means change from baseline (95% CI)	[redacted]	[redacted]

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Change from Baseline in Height at Year 5	External Control (Primary) (N = 98)	Vosoritide 15 µg/kg (N = 10)
Difference in LS means change from baseline	[redacted]	
2-sided p-value	[redacted]	

CI, confidence interval; LS, least square; max, maximum; min, minimum; SD, standard deviation. Results were based on an ANCOVA model with fixed effects of treatment and indicator variables for matching. Source: BioMarin 2020, Natural history integrated analyses report [33]

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19. Appendix G Extrapolation

19.1 Exploratory analyses on height at age 16 years

To understand the potential treatment effect on final height, individual subject's height was extrapolated from the last height assessment at the data cut-off to the time when the subject reaches 16 years of age. At the time of the data cut off the 10 subjects ages ranged from 11 to 16 years. Extrapolated mean results were compared to the mean height of 16-year-old males and females from the Primary NH Descriptive Population. Different assumptions were applied for the extrapolated growth ranging from the best-case scenario that subjects continued to grow at the same rate at the time of the data cut to the worst-case scenario that the subjects grew no more after the time of the data cut off. Height differences of up to 20 cm could be observed in favor of subjects in the vosoritide group at the age of 16 years compared with the external control (Appendix Table 74), and in the worst case scenario where the subjects no longer grew (last observed carried forward [LOCF]), there was a difference of 8.71 cm compared between subjects in the vosoritide group to the external control.

Appendix Table 74. Summary of extrapolated Near Final Adult Height at age of 16 years old analysis population: Vosoritide arm (111-205 Cohort 3) and AchNH descriptive analysis population.

Source: BioMarin, Natural History Integrated Analyses Report. 2020 [33]

20. Appendix H Literature search for HRQoL data

Not Applicable.

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21. Appendix I Mapping of HRQoL data

Not Applicable

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22. Appendix J Probabilistic sensitivity analyses

Appendix Table 75. Parameter distributions applied in the probabilistic sensitivity analyses

Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Treatment discontinuation (annual probability)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$60
Missed doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$62
Relative risk (mortality): Sleep apnoea surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'EfficacyInputs'!$I$162
Relative risk (mortality): Spinal stenosis surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'EfficacyInputs'!$I$163
Relative risk (mortality): Cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'EfficacyInputs'!$I$167
Relative risk (mortality): Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'EfficacyInputs'!$I$168
Relative risk (mortality): Chronic pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'EfficacyInputs'!$I$169
Relative risk (mortality): Foramen magnum stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'EfficacyInputs'!$I$180
Relative risk (CVD): Sleep apnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'EfficacyInputs'!$I$193
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$51
Event.Cost Foramen magnum stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$68
Event.Cost Hydrocephalus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$69
Event.Cost Sleep apnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$70
Event.Cost Spinal stenosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$71
Event.Cost Kyphosis/Lordosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$72

Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Event.Cost Leg bowing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$73
Event.Cost Obesity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$74
Event.Cost Cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$75
Event.Cost Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$76
Event.Cost Chronic pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$77
Event.Cost Otitis media	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$78
Event.Cost Hearing loss/Deafness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$79
Event.Cost Dental malocclusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$80
One-off Cost Sleep apnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$92
One-off Cost Hearing loss/Deafness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$101
Recur.Cost Sleep apnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$I$92
Recur.Cost Obesity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$I$96
Recur.Cost Cardiovascular disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$I$97
Recur.Cost Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$I$98
Recur.Cost Chronic pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$I$99
Recur.Cost Hearing loss/Deafness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$I$101
Dietician	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$166
ENT physician and/or surgeon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$167

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Emergency doctor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$168
General practitioner	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$169
Geneticist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$170
Neurologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$171
Neurosurgeon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$172
Occupational therapist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$173
Ophthalmologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$174
Orthopedic surgeon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$175
Other surgeon, other professional	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$176
Paediatrician	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$177
Physiotherapist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$178
Respiratory physician	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$179
Speech therapist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$180
Cardiologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$181
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$143
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$146
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$147
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$151

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$152
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$153
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$154
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Costs'!$H$155
Disutility: Decompression surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$84
Disutility: Shunt insertion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$85
Disutility: Surgery - Spine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$87
Disutility: Surgery - Kyphosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$88
Disutility: Surgery - Osteotomy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$89
Disutility: Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$91
Utility weight: Sleep apnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$107
Utility weight: Surgery - Spine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$108
Utility weight: Surgery - Kyphosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$109
Utility weight: Surgery - Osteotomy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$110
Utility weight: Obesity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$111
Utility weight: Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$112
Utility weight: Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$113
Utility weight: Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$114

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Utility weight: Tympanostomy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$115
Utility weight: Hearing Impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$116
Utility weight: Surgery - Dental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$117
DCS: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$21
DCS: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$22
DCS: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$24
Shunt insertion: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$143
Shunt insertion: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$146
Sleep apnoea: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$265
Sleep apnoea: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$266
Sleep apnoea: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$268
Sleep apnoea: Annual probability [41 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$269
Spine surgery: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$388
Spine surgery: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$390
Spine surgery: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$391
Spine surgery: Annual probability [41 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$392
Kyphosis - Surgery: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$511
Kyphosis - Surgery: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$512

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Name	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Kyphosis - Surgery: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$513
Kyphosis - Surgery: Annual probability [41 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$514
Tibial osteotomy: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$632
Tibial osteotomy: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$633
Tibial osteotomy: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$634
Tibial osteotomy: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$635
Limb lengthening: Annual probability [20 to 20]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$755
Cardiovascular disorder ACH: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$876
Cardiovascular disorder ACH: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$877
Cardiovascular disorder ACH: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$879
Cardiovascular disorder ACH: Annual probability [45 to 54]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$881
Cardiovascular disorder ACH: Annual probability [55 to 64]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$882
Cardiovascular disorder ACH: Annual probability [65 to 74]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$883
Cardiovascular disorder ACH: Annual probability [75 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$884
CVD AS: Annual probability [22 to 48]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DI$899
CVD AS: Annual probability [49 to 58]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DI$900
CVD AS: Annual probability [59 to 68]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DI$901
CVD AS: Annual probability [69 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DI$902

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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Depression ACH: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1000
Depression ACH: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1001
Depression ACH: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1002
Depression ACH: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1003
Depression ACH: Annual probability [41 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1004
Depression AS: Annual probability [12 to 17]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$CJ$1019
Depression AS: Annual probability [18 to 39]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$CJ$1020
Depression AS: Annual probability [40 to 59]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$CJ$1021
Chronic pain ACH: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1122
Chronic pain ACH: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1123
Chronic pain ACH: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1124
Chronic pain ACH: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1125
Chronic pain ACH: Annual probability [41 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1126
Tympanostomy: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1244
Tympanostomy: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1245
Tympanostomy: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1246
Hearing impairment ACH: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1367
Hearing impairment ACH: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1368

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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Hearing impairment ACH: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1369
Hearing impairment ACH: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1370
Hearing impairment ACH: Annual probability [41 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1371
Hearing impairment AS: Annual probability [0 to 1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DG$1385
Hearing impairment AS: Annual probability [2 to 14]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DG$1386
Hearing impairment AS: Annual probability [15 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DG$1387
Dental malocclusion: Annual probability [0 to 4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1489
Dental malocclusion: Annual probability [5 to 10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1490
Dental malocclusion: Annual probability [11 to 15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1491
Dental malocclusion: Annual probability [16 to 40]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$G$1492
Probability of shunt revision per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$114
Maximum number of shunt revisions per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$115
Percentage of patients that require sleep apnoea surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$125
Percentage of patients in which sleep apnoea is resolved due to surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$126
Maximum number of subsequent CVD events (excluding death) over a lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$157
Annual probability of subsequent CVD event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$156
Probability of subsequent tube placements per year (0-10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$175
Maximum number of tube placements per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$176

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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Percentage of patients in which hearing loss is resolved after 18 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Controls'!$G$180
Sleep apnoea AS: Annual probability [30 to 39]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DJ$298
Sleep apnoea AS: Annual probability [40 to 49]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DJ$299
Sleep apnoea AS: Annual probability [50 to 59]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DJ$300
Sleep apnoea AS: Annual probability [60 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$DJ$301
Stenosis AS: Annual probability [0 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$BG$416
Chronic pain AS: Annual probability [9 to 26]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$BN$1157
Chronic pain AS: Annual probability [27 to 39]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$BN$1158
Chronic pain AS: Annual probability [40 to 49]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$BN$1159
Chronic pain AS: Annual probability [50 to 59]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$BN$1160
Chronic pain AS: Annual probability [60 to 69]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$BN$1161
Chronic pain AS: Annual probability [70 to 100]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$BN$1162
Tympanostomy AS: Annual probability [2 to 8]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$CF$1286
Orthodontics AS: Annual probability [10 to 16]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'IncidenceCalc'!$CH$1523
Utility benefit from exceeding disabilitating height	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$G$145
Utility coefficient - quadratic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$L$18
Utility coefficient - linear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	'Utilities'!$L$19

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