27 January 2022
EMA/5898/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Voxzogo

vosoritide

Procedure no: EMEA/H/C/005475/P46/007

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	29.11.2021	29.11.2021	☐
☐	CHMP Rapporteur Assessment Report	03.01.2022	28.12.2021	☐
☐	CHMP members comments	17.01.2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20.01.2022	n/a	☐
☒	CHMP adoption of conclusions:	27.01.2022	27.01.2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On November the 15th 2021, the MAH submitted the final study report from the completed paediatric study BMN 111-901 for Assessment, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This trial was not part of a specific obligation during the approval procedure.

Insofar, submission is for completeness of information mainly and no changes in product information or the EPAR are foreseen or applied.

2. Scientific discussion

2.1. Information on the development program

Study 111-901 is an observational, multicenter, multinational study that prospectively collected specific growth measurements on pediatric subjects (age: 0 to 17 years) with documented achondroplasia (ACH), based on physical features and radiographic findings and confirmed by genetic testing, being considered for subsequent enrollment in future vosoritide studies sponsored by The MAH. A total of 363 subjects participated in the study.

The 111-901 clinical study report is submitted under Article 46 and is provided in Module 5.3.5.4. No vosoritide or any other study drug was administered as part of the study.

The MAH stated that Study 111-901 is a stand alone study as part of the clinical development program for a product indicated and approved only for the paediatric population (until growth is completed).

This trial was a multicenter, multinational study to collect baseline growth measurements on pediatric subjects with ACH being considered for subsequent enrollment in future studies sponsored by the MAH. In order to obtain accurate baseline measurements, at least 6 months of growth measurements were being collected (or at least 3 months for some subjects aged 0 to < 3 months at study entry).

Data gathered from this study was used to characterize baseline growth data in children or infants (defined as children < 2 years of age) who were subsequently enrolled in future studies sponsored by The MAH, and was also used to establish a historical control cohort for use in other The MAH-sponsored drug-treatment studies, when appropriate.

The MAH believes that neither the EU RMP nor the EU PI are impacted by these results. No changes are applied.

2.2. Information on the pharmaceutical formulation used in the study

No study drug was administered.

2.3. Clinical aspects

2.3.1. Introduction

2.3.2. Clinical study

Protocol No. 111-901: A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia

Clinical study BMN 111-901 " A Multicenter, Multinational Clinical Assessment Study for Pediatric Patients with Achondroplasia

Description

Trial BMN 111-901 is a prospective, multicenter, multinational **observational study** that collects **specific growth measurements on pediatric subjects with ACH being considered for subsequent enrollment in future studies** sponsored by the MAH. Approximately 500 subjects from birth to ≤ 17 years of age at study entry were to be enrolled, with approximately equal numbers of boys and girls.

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 The MAH study), discontinuation of participation, or termination of the study. Subjects who did not enroll in a subsequent The MAH drug-treatment study could choose to continue participating in Study 111-901 for up to 7 years.

No study drug was administered.

Methods

Study participants

Male or female subjects with ACH from birth to ≤ 17 years of age at study entry.

Inclusion Criteria for Enrollment

Individuals eligible to participate in this study had to meet all of the following criteria:

1. 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.
2. Birth to ≤ 17 years of age at study entry.
3. Had ACH, documented by clinical diagnosis.
4. Were ambulatory and able to stand without assistance (not applicable for children who were younger than 5 years of age and less than 104 cm in length).
5. Were willing and able to perform all study procedures as physically possible.

Exclusion Criteria for Enrollment

Individuals who met any of the following exclusion criteria were not eligible to participate in the study:

1. Had hypochondroplasia or short stature condition other than ACH (eg, trisomy 21, pseudo-achondroplasia).
2. Had any of the following disorders:
    - Hypothyroidism
    - Insulin-requiring diabetes mellitus
    - Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others)
    - Inflammatory bowel disease

- Autonomic neuropathy

3. Had an unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression.
4. Growth plates had fused.
5. Had a history of any of the following:
    - Renal insufficiency
    - Anemia
6. Had a history of cardiac or vascular disease, including the following:
    - Cardiac dysfunction
    - Hypertrophic cardiomyopathy
    - Congenital heart disease
    - Cerebrovascular disease, aortic insufficiency
    - Clinically significant atrial or ventricular arrhythmias
7. Current treatment with antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calciumchannel blockers, cardiac glycosides, systemic anticholinergic agents, any medication that may have impaired or enhanced compensatory tachycardia, drugs known to alter renal function that was expected to continue for the duration of the study.
8. Had been treated with growth hormone, insulin-like growth factor 1 (IGF1), or anabolic steroids in the previous 6 months or long-term treatment (> 3 months) at any time
9. Had had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma was acceptable) in the previous 12 months.
10. Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever was longer, before the Screening visit.
11. Had used any other investigational product or investigational medical device for the treatment of ACH or short stature.
12. Planned or expected bone-related surgery (ie, surgery involving disruption of bone cortex) during the study period. Subjects with previous bone-related surgery may have been enrolled if surgery occurred at least 12 months prior to the study and healing was complete without sequelae.
13. Planned or expected to have limb-lengthening surgery during the study period. 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.
14. Had any condition that, in the view of the Investigator, placed the subject at high risk of poor compliance with the visit schedule or of not completing the study.
15. Concurrent disease or condition that, in the view of the Investigator, would have interfered with study participation.

Treatments

N/A (No study drug was administered.)

Objective(s)

To collect baseline growth measurements on pediatric subjects with achondroplasia (ACH). Subjects with at least 6 months of growth data were considered for possible participation in future drug-

treatment studies sponsored by The MAH (for subjects aged 0 to < 3 months at study entry, a minimum of 3 months of data were required).

Outcomes/endpoints

Criteria for Evaluation:

Medical history: Medical history was obtained and included specific information concerning any prior or existing medical conditions and ACH-related symptoms and elicited all major illnesses, diagnoses, and surgeries.

Anthropometric measures: Measures may have included (but were not limited to) standing height, sitting height, weight, head circumference, upper and lower arm length, leg length, and arm span, body mass index (BMI, calculated).

Tanner Stage: Tanner Stage of Pubertal Development was assessed for subjects aged 5 years and older to determine whether the subject had progressed to puberty.

Health-related quality of life (HRQoL), functional independence measures and activities of daily living (ADL): Pediatric Quality of Life Inventory (PedsQL), Quality of Life in Short Statured Youth (QoLISSY), Functional Independence Measure (WeeFIM)® and ADL, Child Behavior Checklist (CBCL), Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), Infant Toddler Quality of Life Questionnaire (ITQoL).

Other: Adverse events (AEs), vital signs, physical examination, concomitant medications, bone metabolism, genomic, and exploratory biomarkers, vitamin D, alkaline phosphatase (ALP), pulse oximetry and ACH-related symptoms, tests, and interventions.

Sample size, Randomisation and blinding (masking)

N/A

Statistical Methods

The analysis population for all outputs was the full analysis set (FAS). The FAS for 111-901 was defined according to the intent-to-treat principle and included all enrolled subjects with a signed informed consent.

The following formats were used for the summary outputs:

1. For the following parameters AGV, height Z-scores, and upper to lower body segment ratio subjects were classified according to the study that the subject enrolled into: BMN 111-202, BMN 111-206, BMN 111-301. Subjects who did not enter another BMN 111 study were classified as "not enrolled". Summary outputs were presented by study and overall category. With the exception of AGV (Section 9.7.1.3.1) outputs were presented for both baseline and each 6-month post-baseline follow-up visit according to these categories. No plots were provided for this summary (see the SAP, Appendix 16.1.9, for visit windowing specifications).
2. All growth parameters were categorized by integer age (0, 1, 2 to maximum year of age) at the time of the assessment. These summaries were presented by sex and overall (see the SAP, Appendix 16.1.9, for age windowing specifications). Box plots of the absolute measures were plotted for each year of age for each sex separately. Spaghetti plots of standing height, height Z-Scores, and upper to lower body segment ratio were plotted by age. Separate plots were

produced by study and sex, for all subjects having at least a 24 month follow-up assessment. The height plots included age-sex specific reference ranges for average stature children (CDC, 2019a) and age-sex specific reference ranges for short stature children (Hoover-Fong, 2008). These plots included all height assessments for height, Z-scores, and upper to lower body segment ratio.

- Data were pooled across sites for all analyses.
- Data were not being presented separately by site in summaries.
- For all statistical summaries, missing data were not imputed.

Growth parameters and analyses:

- Endpoints were presented according to the study that the subject enrolled into: Study 111-202, 111-206, or 111-301. Subjects who did not/or had not yet entered another vosoritide study were presented as "not enrolled". Summary outputs also included an overall category.
- Annualized growth velocity (AGV), height Z-scores, and upper to lower body ratio were presented by study visit.
- All growth parameters were categorized by age (0, 1, 2 to maximum year of age) at the time of the assessment and were presented by sex and overall.

HRQoL, functional independence, and ADL questionnaires: The scores in HRQoL questionnaires, functional independence, and ADL questionnaires (including PedsQL, QoLISSY, and WeeFIM) were summarized by age at the time of the assessment. CBCL, BSID-III, and ITQoL were listed due to limited available data.

Other endpoints and analyses: AEs, serious AEs (SAEs), AEs leading to study discontinuation, deaths, and ACH-related AEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and/or preferred term (PT) or listed. Adjusted rates (rates adjusted according to the length of follow-up) were also provided.

Results

Participant flow

Following enrolment of last subject in 111-206, the study was terminated by the Sponsor on 11 February 2021.

Overall 363 subjects were enrolled in 111-901 at the time the study was terminated. Of these subjects, 225 (62.0%) enrolled in a subsequent drug study: the majority (121 subjects, 33.3 %) enrolled in 111-301; 35 subjects (9.6%) enrolled in 111-202,

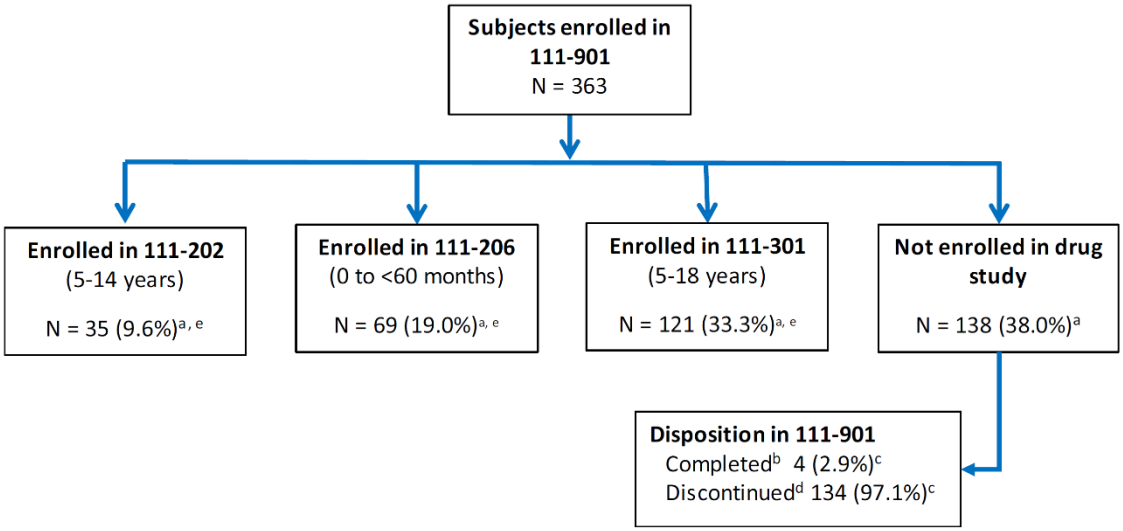
69 subjects (19.0%) enrolled in 111-206, and 138 subjects (38.0%) did not enroll in a subsequent drug study (Figure 10.1.1). Of the 138 subjects who did not enroll into a subsequent drug study, 21 subjects were screening failures in drug studies (7 in 111-202, 11 in 111-206 and 3 in 111-301). Subjects who were screening failures in the drug studies are documented in the relevant CSR for that study. Disposition data are presented by subject in Listing 16.2.1.1 and Listing 16.2.1.2.

Of the subjects who did not enroll into a drug study and discontinued, 26/134 (19.4%) discontinued at the time the sponsor terminated the study, whilst most discontinuations were due to withdrawal by the subject (74 subjects, 55.2 % of all discontinuations from the study) (Table 14.1.1.2); the majority of these were due to personal reasons (such as lack of time, family/child decision, lack of interest, and fear of blood draws, Listing 16.2.1.2). One subject withdrew due to death (further details on this

subject are provided in Section 11.3.6.1.1). Data for subjects who had not enrolled in a subsequent drug study are presented by subject in Listing 16.2.1.4.

As part of Amendment 5 to the protocol, optional diagnostic genetic confirmation of ACH was added to the Schedule of Events for subjects who did not have previous diagnostic genetic testing. Genetic confirmation of ACH diagnosis was required for entry into BioMarin-sponsored drug-treatment trials. Confirmation during the observational study allowed more efficient determination of eligibility for entry into a drug study.

Figure 10.1.1: Subject Disposition: Full Analysis Set



[a] Percentages were calculated using the total number of subjects enrolled as the denominator.

[b] Completed the 111-901 protocol without rolling into a drug study. Subjects completed 5 years study duration under Protocol Amendments 1 and 2, and 7 years study duration under Protocol Amendments thereafter.

[c] Percentages were calculated using the number of subjects not rolled into a drug study.

[d] Discontinued from 111-901 study and not rolled into a drug study.

[e] See SAP for definition of enrolled.

Source: Table 14.1.1.1.

Duration of follow up

The mean (standard deviation [SD]) duration of follow-up overall in 111-901 was 20.41 (14.95) months (ranging from 0.0 to 84.3 months); with a total follow-up of 617.4 patient-years. The mean (range) duration of follow-up in 111-901 ranged from 11.39 (2.2 to 31.2) months for those later enrolling in 111-206, 18.67 (5.7 to 30.3) months for those later enrolled in 111-202, and 20.34 (6.0 to 67.8) months for those later enrolling in 111-301. The duration of follow-up in terms of patient-years was greatest for those that did not enroll in a subsequent drug study (292.4 patient-years, Table 10.1.1).

Final CSR Table 10.1.1: Extent of Follow-up for 111-901 Categorized According to the Drug Study Subjects Later Enrolled into: Full Analysis Set

Extent of Follow-up	111-202 (N=35)	111-206 (N=69)	111-301 (N=121)	Not enrolled in a drug study (N=138)	Overall (N=363)
Duration of follow-up, months[a]					
n	35	6	121	138	363
Mean (SD)	18.67 (6.39)	11.39	20.34	25.42	20.41
Median	18.89	7.23	15.54	24.23	16.53
25th, 75th Percentile	14.49, 21.68	6.01,	10.84,	9.26, 38.97	8.87,
Min, Max	5.7, 30.3	2.2,	6.0, 67.8	0.0, 84.3	0.0, 84.3
Subjects (n, %)[b] with the					
≤6 months	1 (2.9)	17	0	21 (15.2)	39 (10.7)
>6 months	34 (97.1)	52	121	117 (84.8)	324 (89.3)
>6 to ≤12 months	4 (11.4)	26	42 (34.7)	21 (15.2)	93 (25.6)
>12 to ≤18 months	11 (31.4)	11	25 (20.7)	14 (10.1)	61 (16.8)
>18 to ≤24 months	12 (34.3)	7 (10.1)	17 (14.0)	12 (8.7)	48 (13.2)
>24 to ≤30 months	4 (11.4)	6 (8.7)	15 (12.4)	20 (14.5)	45 (12.4)
>30 to ≤36 months	3 (8.6)	2 (2.9)	9 (7.4)	7 (5.1)	21 (5.8)
>36 to ≤42 months	0	0	5 (4.1)	13 (9.4)	18 (5.0)
>42 to ≤48 months	0	0	0	12 (8.7)	12 (3.3)
>48 to ≤54 months	0	0	2 (1.7)	8 (5.8)	10 (2.8)
>54 to ≤60 months	0	0	1 (0.8)	6 (4.3)	7 (1.9)
>60 to ≤66 months	0	0	3 (2.5)	3 (2.2)	6 (1.7)
>66 to ≤72 months	0	0	2 (1.7)	0	2 (0.6)
>72 months	0	0	0	1 (0.7)	1 (0.3)
Extent of follow-up (patient-	54.5	65.5	205.1	292.4	617.4

Source: Table 14.1.11.
Max, maximum; Min, minimum; SD, standard deviation.

[a] Duration of follow-up was defined as (Date of study completion - Baseline date + 1)*12/365.25 for subjects who did not roll over into a drug study and completed Study 111-901, or (Date of study discontinuation - Baseline date + 1)*12/365.25 for subjects who discontinued/rolled over into another study.

[b] Percentages were calculated using the total number of subjects (N for each study) as the denominator.

Recruitment

The original protocol was finalized and approved on 22 December 2011. A summary of the key changes incorporated in the protocol amendments are presented in Table 9.8.1.1.

Key Changes	Rationale
Amendment 1 – 31 January 2013	
Study duration increased from 3 to up to 5 years	To provide more information for historical control cohorts and give children with ACH who enroll in 111-901 the option to participate in subsequent studies
Number of patients enrolled increased from 48 to 200	Allows for accumulation of more data and gives children with ACH who enroll in 111-901 the option to participate in subsequent studies
Upper age range of participants changed from 9 years old to 13.5 years old	Study 111-201 enrolls patients up to 14 years old who have at least a 6-month period of pretreatment growth assessment in 111-901 immediately before study entry; broader age range reflects the general population of ACH patients expected to receive treatment
Inclusion/exclusion criteria revised to correspond to 111-201	To avoid unnecessary exclusion of subjects who elect to participate in 111-201
Prior and concomitant medications criteria have been revised to correspond to Study 111-201.	Revised criteria for prior and concomitant medication use ensure that excluded medications remain consistent for the subjects who elect to participate in Study 111-201.
Evaluation of ALP added to procedures	As a potential earlier marker of treatment efficacy, provides more robust baseline ALP data for patients who subsequently enroll in a treatment study, and may establish an ALP reference range in ACH patients
Height from sole of foot to symphysis pubis; and ratios for upper-to-lower body segment, upper-to-lower extremity, and sitting-to- standing height have been removed from the Schedule of Events table	These evaluations are calculated measurements rather than procedures. The study sites are not responsible for the calculations.
Additional detail on timepoints and patient's position for blood pressure measurements included	Ensures more robust and consistent vital sign data
Differences between growth measures changed from 1 cm to 0.5 cm for all except head circumference (0.3 cm)	Decreasing range of acceptable values may provide increased accuracy and reliability
Measurement time window changed from ± 1 hour to ± 2 hours, and visit windows every 3 months changed from ± 5 days to ± 10 days.	To allow more flexibility for the patients. Changes are not clinically relevant that will affect measurement data.
Amendment 2 – 05 August 2016	
Inclusion criterion "Aged 0 months to 13.5 years, inclusive, at study entry" changed to: "Aged 3 months to 13.5 years, inclusive, at study entry	In real-life clinical practice, it would be very uncommon for a child to be diagnosed with ACH before the age of 3 months
Exclusion criteria regarding bone-related and limb-lengthening surgery revised	Language revised to clarify the time frame before which a previous bone-related surgery is exclusionary for enrollment in this study
All anthropometric measurements except weight performed in triplicate rather than in duplicate	For greater accuracy and reproducibility and to ensure consistency with future BioMarin studies

Collection of some anthropometric measurements (including chest circumference, head length, waist circumference, total hand length, palm and middle finger length, palm width, foot length and width) discontinued	Decreasing the number of anatomical areas being measured reduces the burden to the subject and site and ensures consistency with measurements collected in future BioMarin studies
Collections of HRQoL and ADL added to procedures	Strong supporting evidence to include PedsQL and QoLISSY in 111-901. Both are relevant, have good internal consistency, are relatively easy to use, and collect information on the burden of medical complications in ACH. WeeFIM considers the child's performance from a caregiver's perspective so gives an indication of "burden of care" for families and caregivers of children with ACH. Addition provides consistency between 111 studies and allows potential comparison between studies
Collection of bone metabolism biomarkers and optional biomarkers added to procedures	In order to understand biomarker levels, changes over time, and potential relationships with growth velocity in subjects with ACH and to identify and study potential genetic variants that may modify ACH
Blood pressure measured in sitting and standing positions only at screening. At all other visits, blood pressure measured in a sitting position only	Reduces site and subject burden. 111-901 is a non-interventional study, therefore the risk of blood pressure changes is low
Timing of Tanner Stage assessment changed from every 3 months to every 6 months	To reduce site and subject burden
Age of assessment for Tanner stage changed from "subjects aged 5 to 13.5 years (inclusive)" to "subjects age 5 years and older	13.5 years of age is the upper limit for age at time of study entry, and there is a potential for a subject to become older than 13.5 years during the course of the study. Change allows Tanner stage assessments to continue to be performed.
Amendment 3 – 15 May 2017	
Length of the study increased from 5 to 7 years	To allow continued collection of baseline growth measurements on pediatric subjects, enable eligible subjects in 111-901 to be considered for possible participation in future studies sponsored by BioMarin
Inclusion criterion regarding the age of study participants revised. "Aged 3 months to 13.5 years, inclusive, at study entry" changed to: "Birth to <17 years of age"	To align the age range with ongoing and planned studies
Amendment 4 – 05 October 2017	
Number of subjects planned for the study increased from approximately 250 to approximately 350	To support the ongoing clinical development of the molecule
Inclusion criterion language modified to allow patients ≤ 17 years of age (had previously been < 17 years of age)	Clarify that subjects are eligible up to when they turn age 18.
Language stating subjects aged birth to < 4.5 years may also be enrolled, timing at discretion of the sponsor removed	Enrollment of subjects < 4.5 years has been ongoing without any limitations.

Blood sampling for genomic biomarker analysis language changed from "a single whole blood draw will be collected" to "blood will be collected"	Blood draw may occur at the same time as other blood samples are being taken and more than one blood draw may be required
Amendment 5 – 29 August 2018	
Number of subjects planned increased from approximately 350 to approximately 500	To support the ongoing clinical development of the molecule
For subjects < 3 months old at study entry, minimum observation requirement for growth baseline data changed from 6 to 3 months	Requirement changed so that eligible subjects ranging from 0 to < 3 months at study entry may be considered for participation in a BioMarin-sponsored drug-treatment study
Definition of completion of the study has been clarified	Enrolled subjects must participate until (1) reaching the end of the protocol or (2) enrolling in another BioMarin-sponsored study
Positioning for taking of blood pressure measurements for infants who may be too young to independently sit or stand has been clarified	Study now enrolling infants who may not be able to sit or stand on their own; thus, new instructions for positioning during blood pressure testing were provided
ITQoL, CBCL, and BSID-III assessments added at selected sites enrolling subjects in a BioMarin-sponsored drug-treatment study	Added to augment baseline patient-reported outcome data in the pediatric ACH subject population
Optional diagnostic genetic confirmation of ACH added to Schedule of Events	Genetic confirmation of ACH diagnosis required for entry into BioMarin sponsored drug-treatment trials. Confirmation during 111-901 may allow more efficient determination of eligibility for entry into a drug-treatment study
Laboratory assessments at the End of Study visit not needed for subjects who were enrolling in a BioMarin-sponsored drug- treatment study	Eliminates duplicate blood draws and eases patient burden

Protocol deviations

Overall, 316/363 subjects (87.1%) had at least one protocol deviation and 75 subjects (20.7%) had at least one major protocol deviation (there was a total of 120 major protocol deviations, Listing 16.2.2). Most major protocol deviations were related to a procedure that was not performed; 101/120 reported in 60 subjects; of these 42/101 were reported as due to COVID-19. The remaining major deviations were related to eligibility (7/363 subjects), out of window assessments (13/363 subjects), and use of excluded concomitant medication (1/363). The eligibility protocol deviations included prior bone surgery (n = 4), planned or expected bone-related surgery during the study (n = 1), presence of autoimmune disease (, n = 1), and presence of intra-atrial septum defect (n = 1), two of which led to withdrawal after identification of the deviation (autoimmune disease [n = 1] and presence of intra-atrial septum defect [n = 1]). As defined by the protocol, the use of growth hormone was prohibited during the study. However, one subject received intramuscular Gonapeptyl (triptorelin acetate) for approximately 4 months (between Study Days 268 and 401) in an effort to delay puberty; this subject later enrolled in 111-301, and one subject received growth hormone (somatropin) from Study Day 47; this subject did not enroll into a drug study and discontinued from 111-901 on Study Day 323. One major protocol deviation for out of window assessment resulted in the end-of-study assessments being

taken on 20 September 2018, 8 days after the subject had enrolled into 111-301 and received investigational drug (vosoritide) on 12 September 2018.

CHMP comment:

It should be noted that since the start of the pandemic, 48 subjects had 165 scheduled protocol visits, 13 subjects subsequently enrolled into 111-206 and 35 subjects did not enroll into a drug study. Of the 165 scheduled protocol visits, approximately a fifth were missed (41 visits [24.8%]).

Baseline data

Overall, at the 111-901 baseline, subjects included in this study were aged from newborn to 13.5 years, with a mean (median, range) age of 5.14 (5.09, 0.0 to 13.5) years. Mean (median, range) age by subsequent study enrollment reflected the entry criteria of those studies, with 111-202 and 111-301 enrolling subjects with mean respective ages of 6.62 (6.32, 4.5 to 9.7) and 6.97 (6.48, 2.8 to 13.4) years at the 111-901 baseline and 111-206 enrolling subjects with a mean (range) age of 1.31 (0.98, 0.0 to 4.0) years at the 111-901 baseline. 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) (Final CSR-Table 11.2.1.1).

Final CSR Table: Demographics Categorized According to the Drug Study Subjects Later Enrolled into: Full Analysis Set

Demographic Variable	111-202 (N=35)	111-206 (N=69)	111-301 (N=121)	Not enrolled in a drug study (N=138)	Overall (N=363)
Age at Baseline, years					
n	35	69	121	138	363
Mean (SD)	6.62 (1.65)	1.31 (1.15)	6.97 (2.54)	5.08 (3.35)	5.14 (3.32)
Median	6.32	0.98	6.48	5.10	5.09
Min, Max	4.5, 9.7	0.0, 4.0	2.8, 13.4	0.1, 13.5	0.0, 13.5
Age at Baseline, n (%)a					
< 6 months	0	24 (34.8)	0	17 (12.3)	41 (11.3)
≥ 6 to < 24 months	0	24 (34.8)	0	16 (11.6)	40 (11.0)
≥ 24 to < 60 months	7 (20.0)	21 (30.4)	38 (31.4)	29 (21.0)	95 (26.2)
≥ 5 to < 8 years	19 (54.3)	0	40 (33.1)	49 (35.5)	108 (29.8)
≥ 8 to < 11 years	9 (25.7)	0	33 (27.3)	18 (13.0)	60 (16.5)
≥ 11 to < 15 years	0	0	10 (8.3)	9 (6.5)	19 (5.2)
Sex, n (%)a					
Male	16 (45.7)	37 (53.6)	64 (52.9)	67 (48.6)	184 (50.7)
Female	19 (54.3)	32 (46.4)	57 (47.1)	71 (51.4)	179 (49.3)
Race, n (%)a					
White	23 (65.7)	51 (73.9)	88 (72.7)	110 (79.7)	272 (74.9)
Asian	5 (14.3)	14 (20.3)	21 (17.4)	11 (8.0)	51 (14.0)
					)
Other	2 (5.7)	3 (4.3)	6 (5.0)	10 (7.2)	21 (5.8)
Black or African American	3 (8.6)	0	5 (4.1)	6 (4.3)	14 (3.9)
Islander					

Native Hawaiian or Other Pacific or Not Provided Due to Patient Privacy	2 (5.7)	1 (1.4)	1 (0.8)	1 (0.7)	5 (1.4)
Ethnicity, n (%)a					
Not Hispanic or Latino	33 (94.3)	59 (85.5)	111 (91.7)	123 (89.1)	326 (89.8)
Hispani or Latino or Not Provided Due to Patient Privacy	2 (5.7)	410(15.5	10 (8.3)	0	37 (10.2)

Source: Final CSR-Table 14.1.4.

Max, maximum; Min, minimum; SD, standard deviation.
a Percentages were calculated using the total number of subjects enrolled (N for each study) as the denominator.

The study was conducted by 27 principal investigators at 28 study centers in 8 countries; most subjects participating in the study were at sites in the US (184 subjects [50.7%]), Australia (53 subjects [14.6%]), Spain (44 subjects [12.1%]), and the UK (42 subjects [11.6%]) (Final CSR-Table 14.1.4). The other participating countries were Japan (16 subjects), Germany (11 subjects), France (7 subjects), and Turkey (6 subjects).

Baseline Growth Measures

Weight, BMI, and height Z-scores at the 111-901 baseline were derived using age-sex specific reference data (means and SDS) for average stature children per the CDC (Section 9.7.1.3). Data are presented as SDS above or below the age-specific reference (which is equivalent to 0). Short stature is defined as a height deficit of -2.0 or more SDS below the population-specific mean height for age and gender (Hwang 2015).

As expected in this population, overall mean weight Z-score was -1.56. Mean height Z-scores was -4.63 SDS. Mean BMI Z-score was +2.05 SDS above average; mean upper to lower body ratio was 2.26 (Final CSR-Table 11.2.2.1). With exception of those subjects enrolled into 111-206 (whose differences, such as less height deficit and higher upper to lower body segment ratio, reflect a younger age), baseline characteristics and growth measures were similar across groups by subsequent enrollment, including those not enrolled into a drug study

Final CSR-Table 11.2.2.1: Baseline Characteristics and Growth Measures Categorized According to the Drug Study Subjects Later Enrolled into: Full Analysis Set

Characteristic	111-202	111-206	111-301	Not enrolled in a drug study	Overall
Weight Z-score					
n	35	69	121	138	363
Mean (SD)	-1.47 (1.00)	-1.37 (1.38)	-1.59 (1.26)	-1.65 (1.77)	-1.56 (1.47)
Median	-1.32	-1.26	-1.40	-1.54	-1.40
25th, 75th Percentile	-1.84, -0.91	-2.17, -0.40	-2.38, -0.73	-2.35, -0.68	-2.33, -0.72
Min, Max	-3.7, 1.0	-5.5, 1.4	-4.7, 2.6	-14.2, 2.1	-14.2, 2.6
BMI Z-scorea					
n	35	21	121	105	282
Mean (SD)	2.04 (0.61)	2.73 (0.67)	2.03 (0.79)	1.93 (1.76)	2.05 (1.24)
Median	1.93	2.63	1.99	2.11	2.10
25th, 75th Percentile	1.62, 2.38	2.35, 3.11	1.56, 2.55	1.76, 2.46	1.68, 2.56
Min, Max	1.0, 3.4	1.7, 4.3	-0.4, 4.1	-14.0, 3.9	-14.0, 4.3
Height Z-Score					
n	35	69	121	138	363
Mean (SD)	-5.02 (1.13)	-3.61 (1.41)	-5.11 (1.11)	-4.61 (1.38)	-4.63 (1.39)
Median	-5.01	-3.79	-5.12	-4.78	-4.77
25th, 75th Percentile	-5.78, -4.35	-4.59, -2.52	-5.87, -4.37	-5.44, -3.78	-5.49, -3.81
Min, Max	-7.2, -2.4	-7.1, 0.2	-7.7, -0.8	-9.6, -0.6	-9.6, 0.2
Upper to Lower Body					
n	35	69	121	137	362
Mean (SD)	2.02 (0.20)	2.59 (0.33)	2.12 (0.80)	2.27 (0.49)	2.26 (0.60)
Median	2.00	2.55	2.06	2.16	2.14
25th, 75th Percentile	1.93, 2.12	2.38, 2.75	1.92, 2.19	1.96, 2.38	1.96, 2.40
Min, Max	1.4, 2.5	1.8, 3.5	1.2, 10.5	1.6, 5.3	1.2, 10.5

Source: Final CSR-Table 14.1.5.1. and Final CSR-Table 14.1.5.3.

AGV, annualized growth velocity; BMI, body mass index; CDC, Centers for Disease Control and Prevention; Max, maximum; Min, minimum; SD, standard deviation; WHO, World Health Organization.
Weight and BMI Z-Scores were derived using age-sex specific reference data (means and SDS) for average stature children per the CDC.
Height Z-score was derived using either standing height or body length. The height Z-scores were derived using age-sex specific reference data for average stature children per the Centers for Disease Control and Prevention (CDC) and standard macro, for all ages including
< 24 months (refer to SAP).
Baseline is defined as Day 1 or screening if Day 1 assessment is not available. Baseline AGV is not available since there are
no height assessments taken 6 months prior to entry into this study.
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).
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).
a BMI Z-scores are derived only for subjects older than 24 months who have standing height.
b The negative BMI Z-score in one subject at baseline is discussed in Section 11.3.9.
c For subjects only with body length the crown to rump length is used to determine the upper to lower body ratio.

Baseline Tanner Stage

Overall, most subjects had a Tanner Stage of I at baseline (46.3%); Tanner Stage was not assessed in 48.8%, mainly because subjects were <5 years old (Tanner stage was not done in 1 subject >5 years old) (Final CSR-Table 14.1.5.2). Of those Tanner I at baseline, 100 enrolled into 111-202 (28) or 111-301 (72), while 68 continued in 111-901. A small proportion of subjects who were assessed (18) had a Tanner Stage of > I at baseline; 10 of these subjects subsequently enrolled into 111-301 while 8 remained in 111-901.

Medical History

Overall, 94.2% of subjects had a medical history condition reported at baseline (Final CSR-Table 14.1.6.1) and 87.6% had an ACH-related medical history condition3 reported at baseline (Final CSR-Table 14.1.6.2). Those reported in >10.0% of subjects by preferred term are listed below (all except hyperhidrosis were categorized as ACH-related medical histories [Final CSR-Table 14.1.6.2]).

- **Surgical and medical procedures** (56.7% had any surgical and medical procedure and 54.0% of all subjects had an ACH-related surgical and medical procedure), including ear tube insertion (31.7%), adenotonsillectomy (24.8%), adenoidectomy (13.8%), and spinal decompression (10.5%).
- **Infections and infestations** (56.5% had any infection and infestation and 47.1 % had an ACH-related infection and infestation), including otitis media (41.3 %).
- **Respiratory, thoracic and mediastinal disorders** (53.4% had any respiratory, thoracic and mediastinal disorder and 47.7% had an ACH-related respiratory, thoracic and mediastinal disorder), including sleep apnoea syndrome (40.5%).
- **Musculoskeletal and connective tissue disorders** (49.6% had any musculoskeletal and connective tissue disorder and 49.0% had an ACH-related musculoskeletal and connective tissue disorder), including kyphosis (20.9%), lordosis (14.0%), knee deformity (12.7%), limb deformity (11.6%), and hand deformity (10.2%).
- **Congenital, familial and genetic disorders** (49.0% had any congenital, familial and genetic disorder and 44.6% had an ACH-related congenital, familial and genetic disorder), including congenital bowing of long bones (22.9%), foramen magnum stenosis (14.0%), and skull malformation (10.2%).
- **Nervous system disorders** (33.9% had any nervous system disorder and 30.0% had an ACH-related nervous system disorder), including speech disorder (12.9%).
- **Ear and labyrinth disorders** (25.6% had any ear and labyrinth disorder and 24.5% had an ACH-related ear and labyrinth disorder), including hypoacusis (14.3%).

Based on prior medical history, six subjects had a history of limb lengthening surgery (Final CSR-Table 11.2.4.1); one of which (Subject 0151-1004) was defined as a major protocol deviation due to limb lengthening within 18 months prior to enrollment (according to Protocol Amendment 1 at time of enrollment) (Section 10.2).

Final CSR-Table 11.2.4.2: Medical History (Achondroplasia-Related in ≥ 5.0% Overall): Full Analysis Set

System Organ Class Preferred Term	111-202 (N=35)	111-206 (N=69)	111-301 (N=121)	Not enrolled in a drug study (N=138)	Overall (N=363)
Subjects with any ACH-related medical history condition, n (%)a	**34 (97.1)**	**48 (69.6)**	**113 (93.4)**	**123 (89.1)**	**318 (87.6)**
Surgical and medical procedures, n (%)a	**28 (80.0)**	**18 (26.1)**	**82 (67.8)**	**68 (49.3)**	**196 (54.0)**
Ear tube insertion	21 (60.0)	8 (11.6)	46 (38.0)	40 (29.0)	115 (31.7)
Adenotonsillectomy	19 (54.3)	3 (4.3)	36 (29.8)	32 (23.2)	90 (24.8)
Adenoidectomy	4 (11.4)	7 (10.1)	26 (21.5)	13 (9.4)	50 (13.8)
Spinal decompression	5 (14.3)	2 (2.9)	19 (15.7)	12 (8.7)	38 (10.5)
Tonsillectomy	0	5 (7.2)	9 (7.4)	8 (5.8)	22 (6.1)
Musculoskeletal and connective tissue disorders, n (%)a	**20 (57.1)**	**29 (42.0)**	**50 (41.3)**	**79 (57.2)**	**178 (49.0)**
Kyphosis	6 (17.1)	21 (30.4)	20 (16.5)	29 (21.0)	76 (20.9)
Lordosis	8 (22.9)	4 (5.8)	17 (14.0)	22 (15.9)	51 (14.0)
Knee deformity	5 (14.3)	4 (5.8)	14 (11.6)	23 (16.7)	46 (12.7)
Limb deformity	0	14 (20.3)	8 (6.6)	20 (14.5)	42 (11.6)
Hand deformity	2 (5.7)	13 (18.8)	6 (5.0)	16 (11.6)	37 (10.2)
Pain in extremity	7 (20.0)	0	10 (8.3)	14 (10.1)	31 (8.5)
Joint range of motion decreased	1 (2.9)	8 (11.6)	4 (3.3)	13 (9.4)	26 (7.2)
Cervical spinal stenosis	3 (8.6)	4 (5.8)	7 (5.8)	9 (6.5)	23 (6.3)
Arthralgia	2 (5.7)	0	8 (6.6)	8 (5.8)	18 (5.0)
Respiratory, thoracic and mediastinal disorders, n (%)a	**16 (45.7)**	**29 (42.0)**	**63 (52.1)**	**65 (47.1)**	**173 (47.7)**
Sleep apnoea syndrome	15 (42.9)	27 (39.1)	54 (44.6)	51 (37.0)	147 (40.5)
Snoring	0	5 (7.2)	6 (5.0)	9 (6.5)	20 (5.5)
Tonsillar hypertrophy	0	0	12 (9.9)	8 (5.8)	20 (5.5)
Infections and infestations, n (%)a	**21 (60.0)**	**21 (30.4)**	**66 (54.5)**	**63 (45.7)**	**171 (47.1)**
Otitis media	20 (57.1)	19 (27.5)	57 (47.1)	54 (39.1)	150 (41.3)
Congenital, familial and	**23 (65.7)**	**24**	**48**	**67 (48.6)**	**162 (44.6)**
Congenital bowing of long	19 (54.3)	3 (4.3)	35 (28.9)	26 (18.8)	83 (22.9)
Foramen magnum stenosis	4 (11.4)	8 (11.6)	14 (11.6)	25 (18.1)	51 (14.0)
Skull malformation	1 (2.9)	11 (15.9)	5 (4.1)	20 (14.5)	37 (10.2)
Macrocephaly	0	10 (14.5)	5 (4.1)	15 (10.9)	30 (8.3)
Dysmorphism	2 (5.7)	7 (10.1)	4 (3.3)	12 (8.7)	25 (6.9)
Chondrodystrophy	1 (2.9)	5 (7.2)	4 (3.3)	10 (7.2)	20 (5.5)
Nervous system disorders, n	**13 (37.1)**	**20**	**34**	**42 (30.4)**	**109 (30.0)**
Speech disorder	10 (28.6)	5 (7.2)	14 (11.6)	18 (13.0)	47 (12.9)
Hypotonia	1 (2.9)	7 (10.1)	9 (7.4)	17 (12.3)	34 (9.4)
Hydrocephalus	3 (8.6)	5 (7.2)	1 (0.8)	12 (8.7)	21 (5.8)

Ear and labyrinth disorders, n (%)[a]	**8 (22.9)**	**13 (18.8)**	**36 (29.8)**	**32 (23.2)**	**89 (24.5)**
Hypoacusis	7 (20.0)	5 (7.2)	22 (18.2)	18 (13.0)	52 (14.3)

ACH, achondroplasia; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.
Medical history conditions were coded using MedDRA version 23.0.
Achondroplasia-related PTs were identified prior to database lock via medical review of unique PTs.
a Percentages were calculated using the total number of subjects enrolled (N for each study) as the denominator. Subjects
with more than one medical history condition of the same SOC/PT were counted only once for that SOC/PT.
Source: Final CSR-Table 14.1.6.2.

Prior and Concomitant Medications

A summary of prior medication (defined as any medications taken and ended prior to the baseline visit date) is presented in Final CSR-Table 14.1.8. No subject had received prior treatment with growth hormone.

Most subjects were receiving concomitant medication (defined as any medications taken on or after baseline and included medications initially taken prior to the baseline but continued or ended on or after the baseline visit date) at entry to 111-901 (89.8% overall), with those enrolling later in 111-202 generally having the highest use of concomitant medications (Final CSR-Table 14.1.9). The most frequently used concomitant medications were antibacterials for systemic use (46.3% overall and 51.4% for those enrolling later in 111-202), followed by vitamins (45.7% overall and 48.6% for those enrolling later in 111-202), analgesics (43.5% overall and 25.7% for those enrolling later in 111-202), and anti-inflammatory and antirheumatic products (30.0% overall and 11.4% for those enrolling later in 111-202).

The same pattern was observed for medications newly initiated on-study (86.5% overall), with those enrolling later in 111-202 generally having the highest medication use on study (94.3%) (Final CSR-Table 14.1.10). The most frequently used medications newly initiated on-study were antibacterials for systemic use (45.7% overall and 51.4% for those enrolling later in 111-202), followed by analgesics (41.9 % overall and 25.7% for those enrolling later in 111-202), vitamins (35.0% overall and 42.9% for those enrolling later in 111-202; those enrolling in 111-301 had a higher vitamin use [43.8%]), and anti-inflammatory and antirheumatic products (28.7% overall and 11.4% for those enrolling later in 111-202).

As defined by the protocol, the use of growth hormone was prohibited during the study. However, two subjects received growth therapy. A subject received intra-muscular Gonapeptyl (triptorelin acetate) for approximately 4 months (between Study Days 268 and 401) in an effort to delay puberty; this subject later enrolled in 111-301. A subject received growth hormone (somatropin) during the study (from Study Day 47); this subject did not enroll into a drug study and discontinued from 111-901 on Study Day 323.

Number analysed

It was planned that approximately 500 subjects with ACH would participate in this study. No formal sample size determination was conducted. Approximately equal numbers of males and females were to be enrolled.

Efficacy results

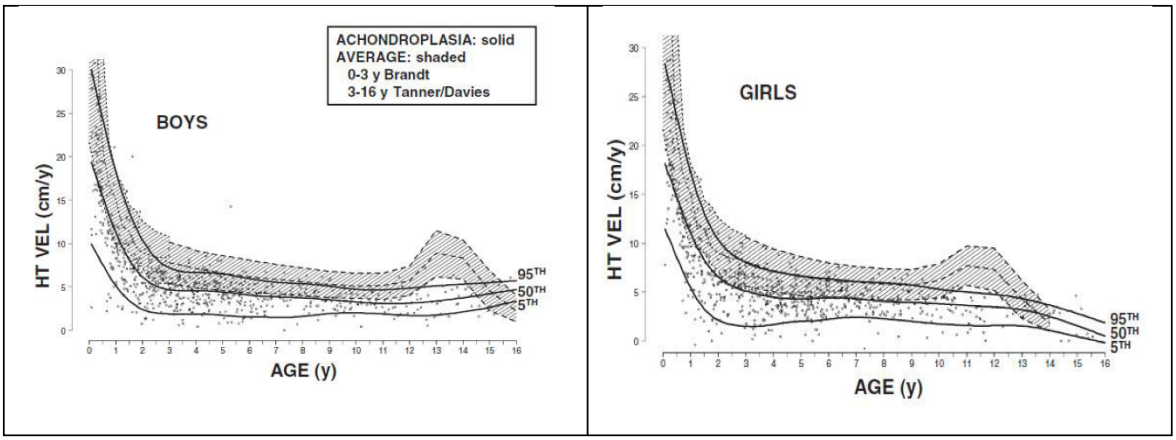
It should be noted that the sample sizes for anthropometric measures decrease with age and particularly for AGV which required pairs of assessments which are 12 months ± 3 apart. The numbers for subjects aged 12, 13, and 14 years become small and should therefore be interpreted with caution.

Growth Parameters:

Annualized Growth Velocity

In average stature children, infancy and puberty are periods of rapid linear growth. In infants, mean AGV is highest shortly after birth (44 cm/year) and thereafter decreases up to age 5 before remaining relatively steady up until puberty (at 5.5 to 7 cm/year). At puberty, average stature children experience a growth spurt with AGV of 8.3 to 9.3 cm/year (Hoover-Fong 2008). Published data has shown the pattern of growth in subjects with ACH is similar to that of average stature children up to puberty however the magnitude of growth is smaller in all age groups (Final CSR-Figure 11.3.1.1.1; Hoover-Fong 2008).

Final CSR-Figure 11.3.1.1.1: Growth Velocity Curves in Boys and Girls Aged 0 to 16 years



HT VEL, height velocity (also referred to as growth velocity); y, years

Height velocity curves (5th, 50th, and 95th percentiles) in boys and girls with achondroplasia aged 0 to 16 years (solid lines) compared with data for children of average stature (dotted and shaded section) from Brandt 1986 (0 to 3 years; 10th, 50th and 90th percentiles) and Tanner and Davies 1985 (3 to 16 years; 3rd, 50th, and 97th percentiles).

Source: Hoover-Fong 2008

Final CSR-Table 11.3.1.1.1: Annualized Growth Velocity (cm/year) by Sex and Age at the Time of Assessment: Full Analysis Set

Age at Assessment Statistics	Male (N=184)	Female (N=179)	Overall (N=363)
0 years			
N	2	8	10
Mean (SD)	14.55 (0.50)	11.62 (1.66)	12.21 (1.92)
Median	14.55	11.65	12.26
25th, 75th Percentile	14.19, 14.90	10.22, 12.92	10.57, 14.04
Min, Max	14.2, 14.9	9.3, 14.0	9.3, 14.9
1 years			
N	11	11	22
Mean (SD)	7.38 (2.08)	7.05 (1.72)	7.22 (1.87)

Median	7.28	7.45	7.43
25th, 75th Percentile	5.48, 8.82	5.09, 8.24	5.48, 8.24
Min, Max	4.6, 10.8	4.1, 9.3	4.1, 10.8
2 years			
N	12	11	23
Mean (SD)	5.46 (0.77)	4.95 (1.43)	5.22 (1.14)
Median	5.60	5.33	5.46
25th, 75th Percentile	5.13, 5.94	3.68, 6.03	4.17, 6.02
Min, Max	4.0, 6.4	3.0, 7.6	3.0, 7.6
3 years			
N	15	15	30
Mean (SD)	5.38 (1.28)	4.89 (0.90)	5.13 (1.12)
Median	5.09	5.06	5.08
25th, 75th Percentile	4.70, 6.70	4.26, 5.41	4.68, 5.47
Min, Max	3.0, 7.6	2.6, 6.4	2.6, 7.6
4 years			
N	28	26	54
Mean (SD)	4.78 (1.20)	4.51 (0.92)	4.65 (1.08)
Median	4.52	4.59	4.54
25th, 75th Percentile	3.89, 5.64	3.88, 5.37	3.88, 5.49
Min, Max	1.9, 7.1	2.5, 5.9	1.9, 7.1
n	38	34	72
Mean (SD)	4.69 (0.97)	4.05 (2.07)	4.39 (1.61)
Median	4.67	4.03	4.47
25th, 75th Percentile	4.06, 5.26	3.70, 4.97	3.75, 5.25
Min, Max	2.7, 6.8	-3.4, 7.0	-3.4, 7.0
6 years			
n	38	45	83
Mean (SD)	4.24 (1.40)	4.14 (0.78)	4.19 (1.10)
Median	4.30	4.15	4.22
25th, 75th Percentile	3.73, 5.15	3.51, 4.64	3.65, 4.81
Min, Max	-2.0, 6.1	2.4, 5.8	-2.0, 6.1
7 years			
n	37	36	73
Mean (SD)	4.03 (0.84)	4.10 (0.91)	4.07 (0.87)
Median	4.05	4.14	4.07
25th, 75th Percentile	3.32, 4.83	3.53, 4.80	3.40, 4.83
Min, Max	2.1, 5.5	1.9, 5.8	1.9, 5.8
8 years			
n	35	25	60
Mean (SD)	3.79 (1.00)	3.99 (0.94)	3.87 (0.97)
Median	3.85	3.75	3.84
25th, 75th Percentile	3.11, 4.35	3.23, 4.36	3.20, 4.36
Min, Max	1.6, 5.9	2.7, 6.2	1.6, 6.2
9 years			
n	27	28	55

Mean (SD)	3.41 (0.73)	3.44 (1.03)	3.43 (0.89)
Median	3.30	3.45	3.32
25th, 75th Percentile	2.84, 4.16	2.57, 4.14	2.71, 4.16
Min, Max	1.8, 4.6	1.5, 5.8	1.5, 5.8
10 years			
n	22	24	46
Mean (SD)	3.62 (0.64)	3.58 (1.29)	3.60 (1.02)
Median	3.50	3.62	3.50
25th, 75th Percentile	3.20, 3.90	2.54, 4.31	2.99, 4.23
Min, Max	2.6, 5.2	1.2, 6.3	1.2, 6.3
11 years			
n	13	13	26
Mean (SD)	3.81 (1.50)	4.23 (0.95)	4.02 (1.25)
Median	3.60	3.82	3.72
25th, 75th Percentile	2.80, 3.82	3.56, 4.84	3.20, 4.84
Min, Max	2.2, 6.9	3.1, 6.0	2.2, 6.9
12 years			
n	8	3	11
Mean (SD)	3.05 (3.24)	3.90 (1.48)	3.28 (2.82)
Median	4.16	4.59	4.50
25th, 75th Percentile	2.55, 5.09	2.21, 4.91	2.44, 5.03
Min, Max	-4.5, 5.3	2.2, 4.9	-4.5, 5.3
13 years			
n	4	3	7
Mean (SD)	3.37 (1.49)	2.40 (1.90)	2.95 (1.61)
Median	2.97	1.38	2.48
25th, 75th Percentile	2.29, 4.45	1.22, 4.59	1.38, 4.59
Min, Max	2.1, 5.4	1.2, 4.6	1.2, 5.4
14 years			
n	2	3	5
Mean (SD)	2.85 (2.37)	1.71 (1.03)	2.16 (1.53)
Median	2.85	1.13	1.17
25th, 75th Percentile	1.17, 4.53	1.09, 2.90	1.13, 2.90
Min, Max	1.2, 4.5	1.1, 2.9	1.1, 4.5

AGV, annualized growth velocity; Max, maximum; Min, minimum; SD, standard deviation.
AGV was derived using standing height. 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).
AGV was derived for all pairs of height assessments 12 months (± 3 months) apart as: ((Height at 12 months - Height at start of 12 months)/(Date at 12 months - Date at start of 12 months)) x 365.25. Age was derived from the integer age at the mid time point for each AGV interval. If a subject had more than one AGV associated to specific integer age then the AGV interval with maximum overlap for that age year is retained, and for equal overlap the one closest to 12 months were selected.
Assessments were excluded on or after limb lengthening or start of growth therapy or start of investigational study drug. Subjects who had limb lengthening prior to the study were excluded.
Source: Final CSR-Table 14.2.1.3.1.

CHMP comment:

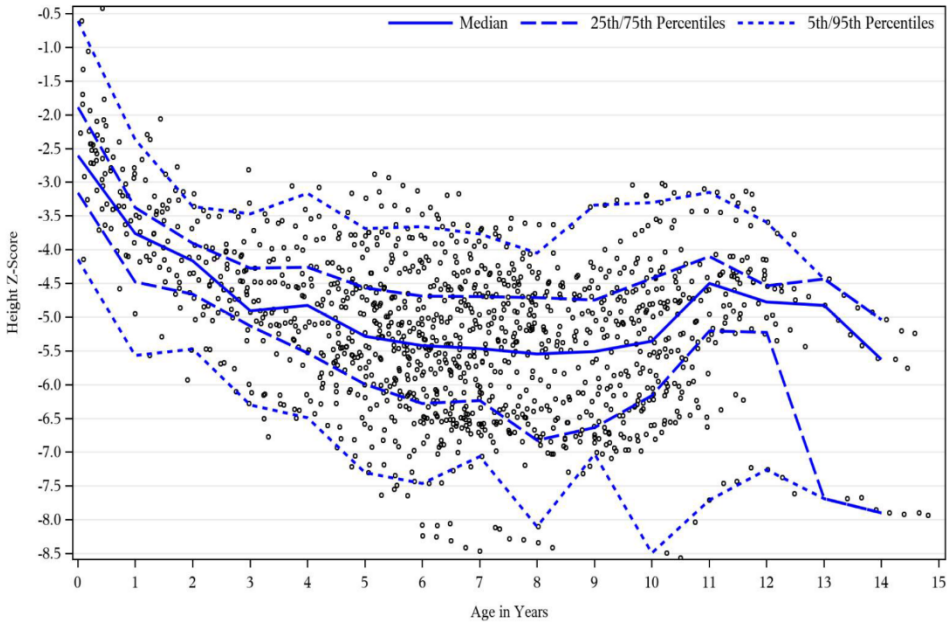
A slight but steady decline in AGV with age was observed and is expected in the ACH population. Median (inter-quartile range [IQR]) AGV in both females and males with ACH enrolled in 111-901 was 11.65 [10.22, 12.92] cm/year for females and 14.55 [14.19, 14.90] cm/year for males) for those aged < 1 year. By 1 year of age, median (IQR) AGV decreased to 7.45 (5.09, 8.24) cm/year in females and 7.28 (5.48, 8.82) cm/year in males. By age 11 years, AGV approximately 4 cm/year for females and males. The number of subjects aged > 12 years was small.

Height Z-score:

Height Z-scores were derived using age-sex specific CDC reference data (means and SDS) for average stature children (Section 9.7.1.3). 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 (Hwang 2015).

For subjects enrolled in 111-901, scatter plots of height Z-scores with median, 5th, 25th, 75th, and 95th percentiles by age at time of assessment are displayed for females (Final CSR-Figure 11.3.1.2.1) and males (Final CSR-Figure 11.3.1.2.2).

Figure 11.3.1.2.1: Scatter Plot with Median, 5th, 25th, 75th, and 95th Percentiles of Standing Height Z-Scores (Using CDC References For All Ages) and Age at the Time of Assessment (Female): Full Analysis Set



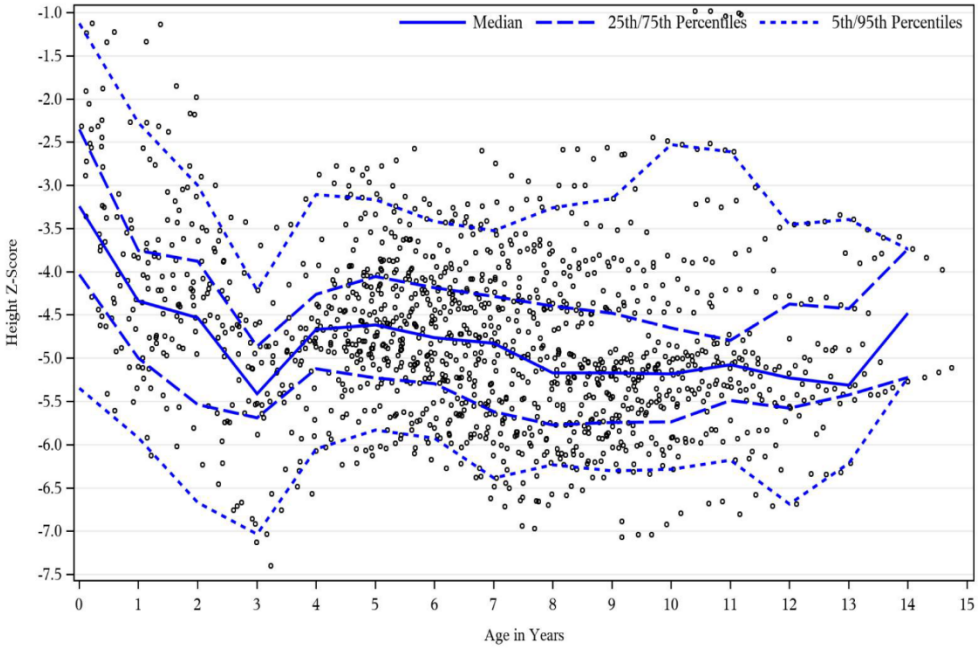
Preferred standing height measurement: body length for ages < 24 months (if not measured, standing height) and standing height for ages ≥24 months (if not measured, body length).

Height Z-scores were derived using age-sex specific reference data for average stature children per the Centers for Disease Control and Prevention (CDC) and standard macro, for all ages including < 24 months (refer to SAP).

For the scatter plot, height Z-scores, scheduled and unscheduled, were included. Median and 5th, 25th, 75th and 95th percentiles were based on the earliest height Z-score for a given integer age. Not all height Z-scores outside of the 5th and 95th percentiles are displayed.

Source: Figure 14.2.2.5a

Figure 11.3.1.2.2: Scatter Plot with Median, 5th, 25th, 75th and 95th Percentiles of Standing Height Z-Scores (Using CDC References For All Ages) and Age at the Time of Assessment (Male): Full Analysis Set



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).

Height Z-scores were derived using age-sex specific reference data for average stature children per the Centers for Disease Control and Prevention (CDC) and standard macro, for all ages including < 24 months (refer to SAP).

For the scatter plot, height Z-scores, scheduled and unscheduled, were included. Median and 5th, 25th, 75th and 95th percentiles were based on the earliest height Z-score for a given integer age. Not all height Z-scores outside of the 5th and 95th percentiles are displayed.

Source: Figure 14.2.2.6a

CHMP comment:

According the data the mean (SD) length deficit in both females and males aged < 1 year is -2.51 [1.04] SDS for females and -3.18 [1.21] SDS for males) compared with average stature children of a similar age; mean length/height deficit increases during 5 years of age (mean [SD] Z-scores of -5.30 [1.08] SDS for females and -4.64 [0.78] SDS for males). Despite increasing variability after 5 years of age, the height deficit remained high for females and males in all age groups throughout the study. This is in accordance with the data reported in the literature.

Standing and sitting height:

Summaries of standing (body length) and sitting height (crown to rump) by age are provided in Final CSR-Table 14.2.4.4.1. In addition, scatter plots of standing height by age and sex are shown in Final CSR-Figure 14.2.4.3a and Final CSR-Figure 14.2.4.4a.

As expected, height values are lower compared to average stature age-sex-specific reference data (from the CDC) (Final CSR-Table 11.3.1.3.1). 111-901 height data in subjects with ACH are consistent with published data in subjects with ACH (Hoover-Fong 2017; Merker 2018) supporting the close resemblance of subjects in 111-901 according to gender and age with the overall ACH population (mean [SD] data across 111-901 and published data are presented in Final CSR-Table 11.3.1.3.2).

Median (IQR) length for subjects aged <1 year for females was 53.53 (50.82, 57.67) cm and for males was 57.30 (53.17, 60.95) cm. Median length/standing height gradually increased by age on study. For subjects aged 13 years the median (IQR) standing height for females was 122.83 (105.60, 126.25) cm and for males was 115.80 (115.30, 122.50) cm (Final CSR-Table 14.2.4.4.1).

Final CSR-Table 11.3.1.3.1: Height/Length-for-Age in Children of Average Stature (CDC 2019b)

	Males			**Females**		
	Percentile Height/length (cm)			**Percentile Height/length (cm)**		
Stage of Growth	**25th**	**50th**	**75th**	**25th**	**50th**	**75th**
Birtha	48.19	49.99	51.77	47.68	49.29	51.02
1 year (11.5-month data)a	73.02	74.92	76.92	71.23	73.19	75.11
2 years (24-month data)b	84.10	86.45	88.81	82.64	84.98	87.31
5 years (59.5-month data)b	105.51	108.63	111.73	104.22	107.37	110.62
10 years (119.5-month data)b	134.02	138.41	142.88	133.31	137.77	142.33
13 years (155.5-month data)b	150.50	155.76	161.08	152.26	156.96	161.63

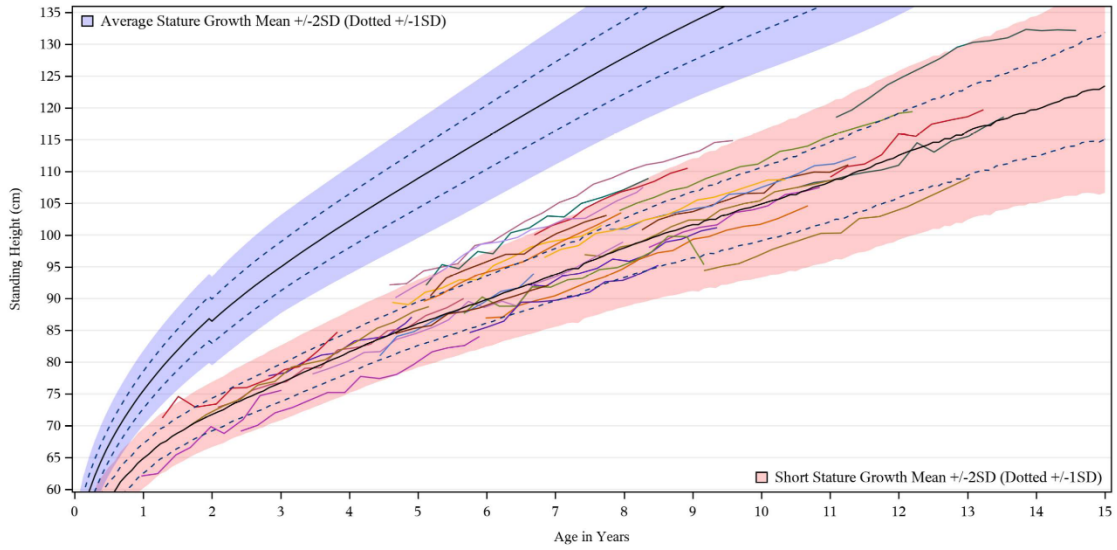
Source: CDC, National Center for Health Statistics, 2001 (CDC 2019b).
a. From Data -Tables of Infant Length-for-age Charts.
b. From Data Tables of Stature-for-age Charts.

Final CSR-Table 11.3.1.3.2: Comparison of Length/Height by Age and Gender in Children with ACH in 111-901 and Children of Average Stature (Hoover-Fong 2017 and Merker 2018)

Age (years)	Males						Females					
	111-901		Published Study		Published Study (Merker 2018)		111-901		Published Study		Published Study (Merker 2018)	
	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)	N	Mean (SD) Height (cm)
1	26	67.06	37	64.9 (2.3)	133	65.9	21	65.78	34	63.9	155	64.6
2	26	73.30	41	71.8 (2.6)	92	72.9	24	72.65	30	70.4	93	71.5
3	25	77.90	38	76.7 (3.0)	63	78.4	27	77.77	37	76.0	69	76.8
4	45	84.49	33	81.7 (3.2)	95	82.9	39	82.99	34	80.9	97	81.4
5	54	87.69	34	86.1 (3.5)	83	87.2	55	86.93	32	85.2	122	85.7
6	55	92.53	30	89.9 (3.7)	84	91.6	59	91.51	32	89.6	85	90.2
7	52	97.29	15	93.8 (4.1)	72	95.8	50	96.12	26	94.0	78	94.4
8	44	101.50	15	98.0 (4.6)	59	99.6	42	99.15	22	97.2	75	98.3
9	41	104.76	19	101.6	59	103.1	38	102.80	14	101.0	65	102.0
10	28	108.31	12	104.9	55	106.2	38	105.72	13	105.0	67	105.7
11	22	112.24	11	108.4	47	109.8	19	111.57	15	107.2	52	109.5
12	14	114.95	10	112.5	43	113.6	8	113.59	6	108.5	50	113.3
13	9	118.71	5	116.3(6.9)	30	117.0	3	118.23	6	113.0	49	116.7
14	2	125.07	4	119.7	37	120.2	3	120.43	4	116.3	34	119.6

SD, standard deviation.
Merker 2018: In the Merker study (2018), the dataset was a mix of cross-sectional and longitudinal data of children of European origin. Most of the height measurements were collected prospectively in the Merker study, and further measurements were collected retrospectively from birth records, child heath, and school records.
Hoover-Fong 2017: In the Hoover-Fong study (2017), the dataset was retrospective longitudinal data of children of US origin. 111-901 data taken from Final CSR-Table 14.2.4.4.1: Standing Height (cm) by Sex and Age at the Time of Assessment.

Not Enrolled into Any Drug Study



Average stature reference was the age-sex-specific reference data per Centers for Disease Control and Prevention. Short stature reference was the age-sex specific reference data from Hoover-Fong 2017.
Preferred use for standing height: body length for ages ≤24 months; if not measured, standing height was used. Standing height for ages > 24 months; if not measured, body length was used. Only subjects with at least a 24-month visit were included.
Source: Figure 14.2.4.2.1, Figure 14.2.4.2.2, Figure 14.2.4.2.3, and Figure 14.2.4.2.4.

CHMP comment:

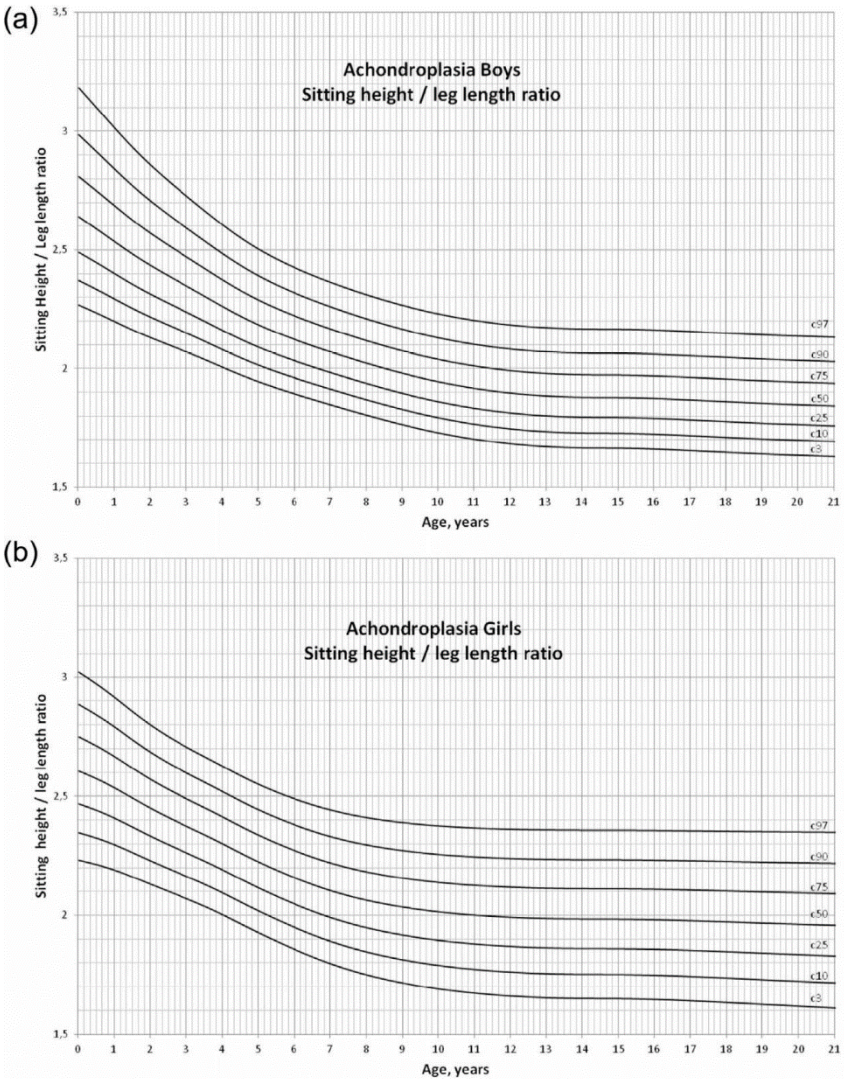
In summary, the median (IQR) length for subjects aged <1 year for females was 53.53 (50.82, 57.67) cm and for males was 57.30 (53.17, 60.95) cm. Median length/standing height gradually increased by age on study. For subjects aged 13 years the median (IQR) standing height for females was 122.83 (105.60, 126.25) cm and for males was 115.80 (115.30, 122.50) cm. Again, this outcome is similary to that reported in the literature.

Upper to lower body segment ratio:

The upper to lower body segment ratio changes from birth to adulthood in a similar fashion for both the general population as well as children with ACH with a decline between 0 and approximately 7 years of age reaching its final value around 10 years of age (Final CSR-Figure 11.3.1.4.1).

The difference between the general population and children with ACH is that the ratio itself differs, with the mean value at birth being 1.7 for the general population which decreases to about 1.1 by 5 to 6 years of age and reaches a final value of 1 by 10 years of age. In contrast, for children with ACH, published data (del Pino 2019, Hoover-Fong 2008) show, the mean value at birth is about 2.6, reaching about 2 at 5 to 6 years of age and plateauing around 1.8 at 10 years (Final CSR-Figure 11.3.1.4.1).

Final CSR-Figure 11.3.1.4.1: Sitting Height to Leg Length Ratio Curves for ACH 0 to 21 years

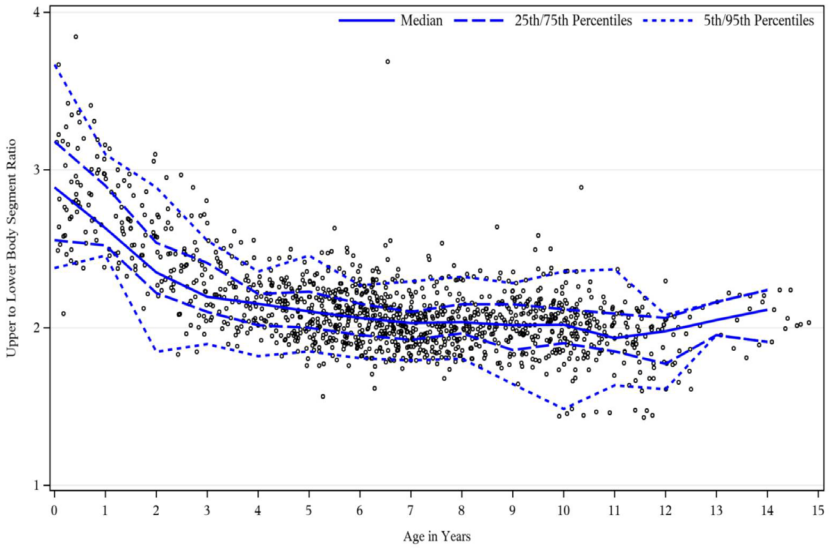


ACH, achondroplasia.
(a) Argentine sitting height to leg length ratio curves for achondroplasia with 3rd, 10th, 25th, 50th, 75th, 90th, and 97th centiles for boys 0–21 years.
(b) Argentine sitting height to leg length ratio curves for achondroplasia with 3rd, 10th, 25th, 50th, 75th, 90th, and 97th centiles for girls 0–21 years.
Source: Del Pino 2019.

For subjects enrolled in 111-901, box plots of upper to lower body segment ratio by age at time of assessment is displayed for females in Final CSR-Figure 14.2.3.1 and for males in Final CSR-Figure 14.2.3.2.

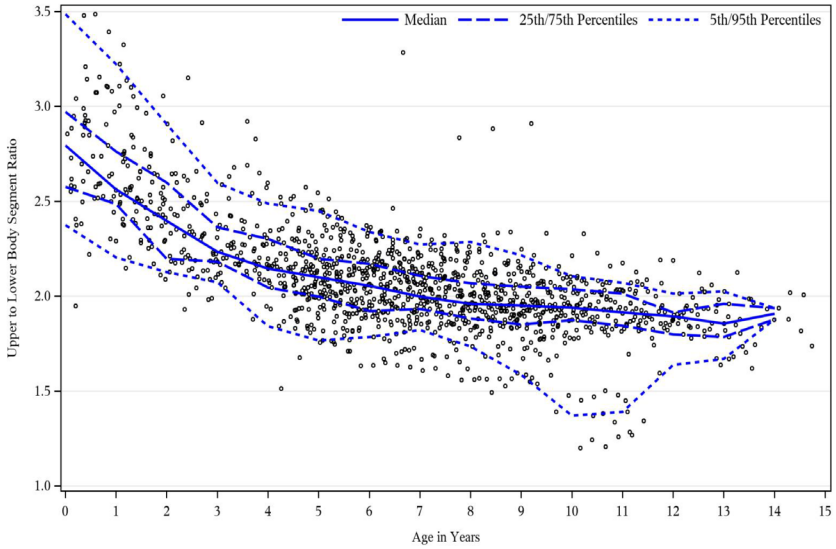
Mean (SD) upper to lower body segment ratio in both females and males was highest for those aged <1 year (respectively 2.94 [0.60] and 2.80 [0.37]) and decreased gradually to approximately 2 for both females and males at 4 years of age. Scatter plots of upper to lower body segment ratio by age and sex are shown in Final CSR-Figure 11.3.1.4.2 and Final CSR-Figure 11.3.1.4.3. One subject had an erroneous body proportion ratio of 10.49 at baseline; the subsequent on-study ratios were between 1.76 and 1.66.

Figure 11.3.1.4.2: Scatter Plot with Median, 5th, 25th, 75th and 95th Percentiles of Upper to Lower Body Segment Ratio and Age at the Time of Assessment (Female): Full Analysis Set



Upper to lower body segment ratio was based on either body length and crown to rump, or standing and sitting height.

Figure 11.3.1.4.3: Scatter Plot with Median, 5th, 25th, 75th and 95th Percentiles of Upper to Lower Body Segment Ratio and Age at the Time of Assessment (Male): Full Analysis Set



Upper to lower body segment ratio was based on either body length and crown to rump, or standing and sitting height.

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).

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).

For the scatter plot all upper to lower body segment ratios, scheduled and unscheduled, were included. Median and 5th, 25th, 75th and 95th percentiles were based on the ratios for a given integer age. Not all ratios outside of the 5th and 95th percentiles are displayed.

Source: Figure 14.2.3.6c.

CHMP comment:

These data show disproportionality in upper to lower body ratio and are consistent with the published data in children with ACH (del Pino 2019, Hoover-Fong 2008). A steep decline from 0 to 3 years was observed followed by a slow decline up to the age of 10 and 12 years for females and males, respectively. Mean (SD) upper to lower body segment ratio in both females and males is highest for those aged <1 year (respectively 2.94 [0.60] and 2.80 [0.37]) and decreases gradually to approximately 2 for both females and males at 4 years of age. This is reported also by other authors

Other body proportion ratios and growth measures:

The following other body proportion ratios and growth measures were summarized:

- Upper arm length to lower arm (forearm) length ratio (Final CSR-Table 14.2.4.1): mean (SD) ratio for subjects aged < 1 year was 1.06 (0.13) and remained similar by age on study; for subjects aged 14 years the mean (SD) ratio was 1.05 (0.10).
- Upper leg length (thigh) to lower leg length ratio (Final CSR-Table 14.2.4.2): mean (SD) ratio for subjects aged < 1 year was 0.68 (0.10) and remained similar by age on study; for subjects aged 14 years the mean (SD) ratio was 0.69 (0.08).
- Arm span to standing height ratio (Final CSR-Table 14.2.4.3): mean (SD) ratio for subjects aged < 1 year was 0.88 (0.03) and remained similar by age on study; for subjects aged 14 years the mean (SD) ratio was 0.91 (0.03).
- Lower body length (Final CSR-Table 14.2.4.6): mean (SD) lower body length for subjects aged < 1 year was 14.52 (2.07) cm and gradually increased by age on study; for subjects aged 14 years the mean (SD) length was 40.67 (4.04) cm.
- Knee to heel length (Final CSR-Table 14.2.4.7): mean (SD) knee to heel length for subjects aged < 1 year was 12.81 (1.29) cm and gradually increased by age on study; for subjects aged 14 years the mean (SD) length was 32.84 (3.12) cm.
- Lower arm (forearm) length (Final CSR-Table 14.2.4.8): mean (SD) lower arm (forearm) length for subjects aged < 1 year was 7.69 (0.91) cm and gradually increased by age on study; for subjects aged 14 years the mean (SD) length was 17.35 (2.69) cm.
- Upper arm length (Final CSR-Table 14.2.4.9): mean (SD) upper arm length for subjects aged < 1 year was 8.08 (0.99) cm and gradually increased by age on study; for subjects aged 14 years the mean (SD) length was 18.13 (2.21) cm.
- Upper leg (thigh) length (Final CSR-Table 14.2.4.10): mean (SD) upper leg (thigh) length for subjects aged < 1 year was 8.69 (1.47) cm and gradually increased by age on study; for subjects aged 14 years the mean (SD) length was 22.80 (3.13) cm.
- Tibial length (Final CSR-Table 14.2.4.11): mean (SD) tibial length for subjects aged < 1 year was 8.22 (1.05) cm and gradually increased by age on study; for subjects aged 14 years the mean (SD) length was 20.34 (2.11) cm.
- BMI Z-score (assessed for subjects ≥24 months) (Final CSR-Table 14.2.4.12): mean (SD) BMI Z-score for subjects aged 2 years was 2.26 (0.93) SDS above average and generally decreased with age to 1.73 (0.70) for subjects aged 14. These data show that BMI is higher in children with ACH than in average stature children and is consistent with published data in ACH (Hoover-Fong 2008).

- Weight Z-score (Final CSR-Table 14.2.4.13): median (IQR) weight Z-score for subjects aged < 1 year was 1.14 (-1.84, -0.37) SDS below average and varied by age with no obvious pattern on study. For subjects aged 12, 13 and 14, median (IQR) weight Z-score was -1.15 (-2.45, -0.55), -0.94 (-2.64, -0.10), and -0.43 (-1.98, 0.16) SDS below average. These data show that weight is lower in children with ACH than in average stature children.

Most subjects assessed had a Tanner Stage of I at time of enrolment. A small number reached Tanner Stage >I on study: subjects aged 7 years (2/106, both female), 8 years (6/90, 4 female:2 male), 9 years (13/83, 11 female:2 male), 10 years (23/65, 20 female:3 male), 11 years (27/45, 16 female:11 male), 12 years (15/22, 6 female:9 male), 13 years (10/12, 3 female:7 male), and 14 years (5/5, 3 female:2 male).

HRQoL, functional independence and ADL questionnaires:

Data collected using the HRQoL, and functional independence and ADL questionnaires (PedsQL, QoLISSY, WeeFIM, CBCL, BSID-III, and ITQoL) were limited as these were introduced later in the study (Protocol Amendment 2).

The **PedsQL** is a clinical outcomes assessment tool to measure HRQoL in children and adolescents. In this study, both children with ACH and their parents/caregivers generally rated the children's quality of life lower compared with a population of average stature children. The exception to this 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 to be similar to the population of average stature children. These findings are consistent with a recent study in a population of ACH subjects (Witt 2019).

Data from the **QoLISSY**, a disease specific patient-reported outcome tool designed for short statured youth, showed that for the physical, social, and emotional domains, values were similar across ages.

Of all five subject-rated domains (physical, social, emotional, coping, and belief), coping scored the lowest. However, coping and belief scores tended to increase for subjects 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. To date, no other QoLISSY data has been published in ACH. Data is available in short stature subjects due to idiopathic short stature and growth hormone deficiency (Bullinger 2015); domain scores reported appear similar to those in 111-901.

Functional performance (self-care, mobility, and cognition) were assessed using the **WeeFIM**. Results showed that functional performance improved with age, however subjects with ACH required greater caregiver assistance (ie, self-care and mobility assistance) for a longer period of time than typically developing children without ACH; these functional differences between children with short stature are expected in an age-matched population (Msall 1994). Social cognition of subjects with ACH was similar to normative data. These findings are consistent with published data in ACH subjects (Ireland 2011).

BSID-III data are limited (as it was included for selected sites only at Protocol Amendment 5). All 3 composite scores (Cognitive, Language, and Motor) were below average across all ages with the greatest deficit observed in the development of motor skills.

ITQoL data are limited (as it was included for selected sites only at Protocol Amendment 5).

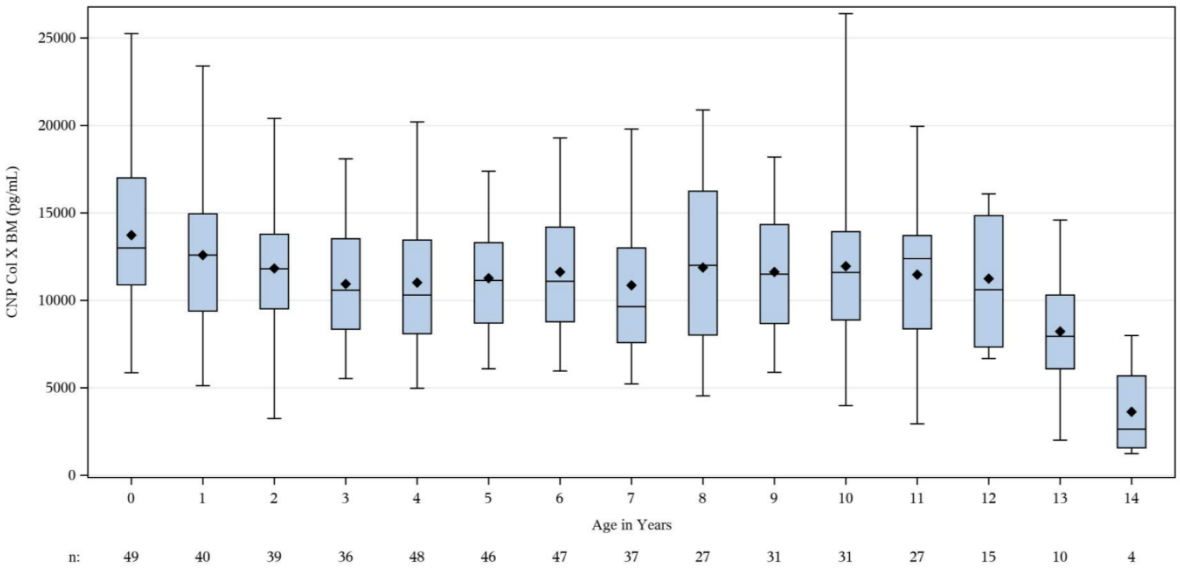
Following birth, there was a trend for overall health, physical ability, and growth and development to decline.

Collagen Type X (CMX)

The bone metabolism biomarker, CXM, is a degradation fragment of type X collagen which is released into the circulation as part of the endochondral ossification process (Coghlan 2017). Serum CXM samples were taken in a total of 245 pediatric subjects with ACH across visits and their ages at the date of assessment ranged from 1 month to 14 years.

The median CXM concentration of each subject was calculated for each year of age to derive a single observation for each subject and year of age (Table 14.3.5.4 and Figure 12.1). The results demonstrate that CXM concentrations in pediatric subjects with ACH are relatively higher (median concentrations around 13,000 pg/mL) in the first two years of life (when growth rates are the fastest) with pronounced variability. CXM concentrations stay relatively consistent with median concentrations around 11,000 pg/mL across 3 to 12 years of age with a slight elevation between 8 and 11 years of age followed by a marked decrease after the age of 13 years (median concentration < 10,000 pg/mL), albeit observed with smaller sample sizes. In general, the concentration of CXM in children with ACH appears to be lower in all ages than, and the high inter-subject variability in CXM concentrations and the overall trend of CXM concentrations level across ages are similar to, that observed by Coghlan *et al* in non-ACH infants and children (Coghlan 2017).

Figure 12.1: Box Plot of Collagen X (pg/mL) by Age at the Time of Assessment: Full Analysis Set



For each year of age, the median of all the assessments while the subject has a specific age is taken.

Box plot displays the 25th and 75th percentiles (box edges), the median (midline), the mean (diamond symbol) and the 2.5th and 97.5th percentiles (whiskers).

Source: Figure 14.3.5.1.4.

Safety results

Overall, 84.0% of subjects (305/363) experienced at least one AE, 10.5% (38/363) experienced an AE of Grade 3 or higher severity, and 14.0% (51/363) experienced at least one SAE. 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 (Final CSR-Table 11.3.5.1.1)

Final CSR-Table 11.3.5.1.1: Overview of Incidence of Adverse Events: Full Analysis Set

AE Category	Overall (N=363)
Subjects with any AE, n (%) a	305 (84.0)
AEs leading to study discontinuation	4 (1.1)
Subjects with any SAE, n (%) a	51 (14.0)
SAEs leading to study discontinuation	3 (0.8)
Subjects with any AE of CTCAE grade ≥ 3, n (%) a	38 (10.5)
Subjects who died, n (%) a	1 (0.3)

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 MedDRA 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 one AE of the same category were counted only once for that category.
Source: Final CSR-Table 14.3.1.1

Final CSR-Table 11.3.5.2.3.1: Incidence and Adjusted Event Rates of Adverse Events by Preferred Term (event rate ≥ 0.02 per person-year): Full Analysis Set

Preferred Term	Overall	
	Incidence n (%)a	Event Rate (person-years) m (rate)b
Subjects with any AE, n (%)a	**305 (84.0)**	**1728 (2.80)**
Upper respiratory tract infection	72 (19.8)	118 (0.19)
Nasopharyngitis	58 (16.0)	90 (0.15)
Otitis media	55 (15.2)	84 (0.14)
Ear infection	55 (15.2)	76 (0.12)
Pyrexia	51 (14.0)	69 (0.11)
Vitamin D deficiency	53 (14.6)	64 (0.10)
Vomiting	26 (7.2)	39 (0.06)
Cough	34 (9.4)	37 (0.06)
Gastroenteritis	28 (7.7)	35 (0.06)
Sleep apnoea syndrome	28 (7.7)	34 (0.06)
Vitamin D decreased	28 (7.7)	34 (0.06)
Fall	19 (5.2)	31 (0.05)
Headache	18 (5.0)	31 (0.05)
Arthralgia	17 (4.7)	28 (0.05)
Pharyngitis	19 (5.2)	28 (0.05)
Teething	14 (3.9)	22 (0.04)
Bronchitis	12 (3.3)	20 (0.03)
Otitis media acute	9 (2.5)	19 (0.03)
Influenza	16 (4.4)	17 (0.03)
Nasal congestion	17 (4.7)	17 (0.03)
Pain in extremity	8 (2.2)	17 (0.03)
Pharyngitis streptococcal	16 (4.4)	17 (0.03)
Back pain	8 (2.2)	16 (0.03)
Conjunctivitis	13 (3.6)	15 (0.02)

Preferred Term	Overall	
	Incidence n (%)a	Event Rate (person-years) m (rate)b
Viral infection	12 (3.3)	15 (0.02)
Bronchiolitis	12 (3.3)	14 (0.02)
Ear pain	9 (2.5)	14 (0.02)
Oropharyngeal pain	12 (3.3)	14 (0.02)
Diarrhoea	11 (3.0)	13 (0.02)
Gastroenteritis viral	10 (2.8)	13 (0.02)
Rhinorrhoea	11 (3.0)	13 (0.02)
Sinusitis	11 (3.0)	12 (0.02)
Rash	10 (2.8)	11 (0.02)
Contusion	7 (1.9)	10 (0.02)
Seasonal allergy	10 (2.8)	10 (0.02)
Tonsillitis	7 (1.9)	10 (0.02)
Viral upper respiratory tract infection	7 (1.9)	10 (0.02)
Rhinorrhoea	11 (3.0)	13 (0.02)
Sinusitis	11 (3.0)	12 (0.02)
Rash	10 (2.8)	11 (0.02)

Final CSR-Table 11.3.5.2.4.1: Incidence and Adjusted Event Rates of Adverse Events of CTCAE Grade ≥ 3: Full Analysis Set

Preferred Term	Overall	
	Incidence n (%)a	Event Rate (person-years) m (rate)b
Total duration of follow-up, person-years	**-**	**617.4**
Subjects with any AE Grade ≥ 3, n (%)a	**38 (10.5)**	**59 (0.10)**
Sleep apnoea syndrome	7 (1.9)	7 (0.01)
Cervical spinal stenosis	4 (1.1)	5 (0.01)
Bronchiolitis	3 (0.8)	4 (0.01)
Foramen magnum stenosis	3 (0.8)	3 (0.00)
Blood alkaline phosphatase increased	3 (0.8)	3 (0.00)
Febrile convulsion	2 (0.6)	2 (0.00)
Hydrocephalus	2 (0.6)	2 (0.00)
Adenoidal hypertrophy	2 (0.6)	2 (0.00)
Tonsillar hypertrophy	2 (0.6)	2 (0.00)
Henoch-Schonlein purpura	1 (0.3)	3 (0.00)
Cardio-respiratory arrest	1 (0.3)	1 (0.00)
Vascular malformation	1 (0.3)	1 (0.00)
Vomiting	1 (0.3)	1 (0.00)
Appendicitis	1 (0.3)	1 (0.00)
Pneumonia	1 (0.3)	1 (0.00)

Preferred Term	Overall	
	Incidence n (%)a	Event Rate (person-years) m (rate)b
Respiratory syncytial virus bronchiolitis	1 (0.3)	1 (0.00)
Soft tissue infection	1 (0.3)	1 (0.00)
Viral upper respiratory tract infection	1 (0.3)	1 (0.00)
Craniocerebral injury	1 (0.3)	1 (0.00)
Joint injury	1 (0.3)	1 (0.00)
Skull fracture	1 (0.3)	1 (0.00)
CSF pressure	1 (0.3)	1 (0.00)
Respiratory syncytial virus test	1 (0.3)	1 (0.00)
Neck pain	1 (0.3)	1 (0.00)
Spinal stenosis	1 (0.3)	1 (0.00)
Arachnoid cyst	1 (0.3)	1 (0.00)
Cerebral haemorrhage	1 (0.3)	1 (0.00)
Cerebral ventricle dilatation	1 (0.3)	1 (0.00)
Cervical cord compression	1 (0.3)	1 (0.00)
Psychogenic seizure	1 (0.3)	1 (0.00)
Spinal cord compression	1 (0.3)	1 (0.00)
Acute respiratory distress syndrome	1 (0.3)	1 (0.00)
Hypoxia	1 (0.3)	1 (0.00)
Sinus congestion	1 (0.3)	1 (0.00)
Wheezing	1 (0.3)	1 (0.00)
Ventriculo-peritoneal shunt	1 (0.3)	1 (0.00)

AE, adverse event; CTCAE, Common Terminology Criteria For Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, preferred term; SOC, system organ class.
AEs with onset or worsening after the start of the study were included. AEs were coded using MedDRA 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 one AE of the same SOC/PT/CTCAE grade were counted only once for that SOC/PT/CTCAE grade.
b Adjusted event rates were calculated by dividing the total number of events (m) by the total duration of the follow-up. 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: Final CSR-Table 14.3.1.2.1.

Deaths

There was **one death during the study; this subject was not enrolled into a drug study.**

A male subject enrolled in 111-901. The subject's concurrent conditions included asthma, cervical cord compression. Foramen magnum stenosis, hypotonia, sleep apnoea syndrome, cerebral ventricle dilatation, joint range of motion decreased, skull malformation, skin hyperpigmentation, macrocephaly, kyphosis, chest X-ray abnormal, atrial septal defect, limb deformity, skeletal dysplasia, and hand deformity. No allergies were reported.

From Study Day 61 to 64, the subject was undergoing screening for the 111-206 study Cohort 3. Screening sleep study showed severe obstructive sleep apnoea with frequent desaturation; screening echocardiogram showed right ventricular hypertrophy; screening MRI showed narrowing of the foramen magnum with no cerebrospinal fluid around the cord, but no abnormal cord signal (no

myelomalacia) and no symptoms or signs of cord compression were found. A neurosurgery evaluation and repeat sleep study were recommended.

At the time of the event, the subject was still in screening and had not received study drug. The subject was at a daycare facility and experienced a Grade 4, life-threatening cardiopulmonary arrest (PT: cardio-respiratory arrest). Emergency medical services (EMS) were called and cardiopulmonary resuscitation (CPR) was performed during transport to a local hospital.

Brain death was declared on Study Day 72. The investigator assessed the event of cardio-respiratory arrest as not related to study drug as the subject had not received vosoritide. The investigator also assessed the event as not related to a study mandated procedure. No other etiological factors were reported.

Summary of safety

Overall, 84.0% of the included subjects (305/363) in this observational study regarding the natural history of the disease experienced at least one AE, 10.5% (38/363) experienced an AE of Grade 3 or higher severity, and 14.0% (51/363) experienced at least one SAE. 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 due to cardio-respiratory arrest which was assessed by the investigator to be not related to study drug as the subject did not received any study drug.

The comorbidities and burden of illness reported in this study (as medical history and AEs on study) are consistent with published literature for children with ACH (Fredwall 2019; Ireland 2014; Horton 2007). These complications include ear, nose and throat complications, sleep apnoea, chronic pain often caused by limb and spine deformities (including stenosis and kyphosis) and neurological complications such as cervical cord compression at the cervicomedullary junction and foramen magnum.

Vitamin D deficiency was a common finding in medical history, and approximately one quarter of subjects had AEs of low vitamin D on the study and initiated concomitant vitamin D. The range of vitamin D values was wide within all age groups. Median vitamin D levels remained within the normal range up to approximately 4 years of age. Thereafter, levels remained either at or below the lower limit of normal.

In this study, systolic and diastolic blood pressure in subjects aged 1 to 4 years is high and would be considered in the hypertensive range compared with sex-, age- and height-matched normative data (Flynn 2017). From 5 years onwards, systolic blood pressure would be considered elevated whilst diastolic blood pressure was within the normal range. Heart rate across all ages was within the normal range.

2.3.3. Discussion on clinical aspects

Study 111-901 was a multicenter, multinational study to prospectively collect baseline growth measurements in pediatric subjects with ACH being considered for subsequent enrollment in future interventional studies with vosoritide, sponsored by the MAH.

A total of 363 subjects with ACH were enrolled with a mean (SD) duration of follow-up of 20.41 (14.95) months (ranging from 0 to 84.3 months). Baseline demographics reflected the epidemiology of ACH and the geographic distribution of recruiting countries; there was a balance of male and female

subjects and the majority were Caucasian. Subjects included in this study were aged from newborn to 13.5 years, with a mean (SD) age of 5.14 (3.32) years. Most subjects were Tanner stage I.

Anthropometric data for this study demonstrate that subjects enrolled in 111-901 have disproportionate short stature and closely resemble similar aged populations with ACH presented in the published literature (Hoover-Fong 2008; Hoover-Fong 2017; Merker 2018; Del Pino 2019). In average stature children, growth velocity during the first years of life is rapid. It then decreases and becomes relatively steady before a second rapid growth spurt during puberty. Although the pattern of growth in subjects in 111-901 up to 12 years was similar to that of average stature children, the magnitude of growth was smaller in all age groups. Consequently, median height in both females and males was lower from birth compared with average stature children and remained low in all age groups throughout the study. The magnitude of the height deficit between 111-901 subjects and average stature children, measured by the height Z-score, increases with age. Pubertal growth in 111-901 could not be evaluated due to the small number of patients in the older age groups (maximum age enrolled was 13.5 years). The standing height data in 111-901 subjects with ACH are consistent with published data in ACH, supporting the close resemblance of subjects in 111-901 according to gender and age with the overall ACH population (Hoover-Fong 2017; Merker 2018).

Consistent with the literature (Hoover-Fong 2008), subjects in 111-901 had a disproportionate upper to lower body ratio and rhizomelic shortening of the arms and legs.

Mean (SD) upper to lower body segment ratio in both females and males was highest for those aged <1 year (respectively 2.94 [0.60] and 2.80 [0.37]) and decreased gradually to approximately 2 for both females and males at 4 years of age. Subjects with ACH have a much greater upper to lower body ratio compared with average stature age-specific reference data. Because the growth of the extremities is limited in ACH relative to the normal growth of the trunk, the ratio of the upper to lower body in subjects with ACH never reaches 1.

Overall, by subject age and gender there were no notable differences in anthropometric data between subjects who later enrolled in a drug study and those who did not enroll in a drug study, thus supporting the lack of bias of subject enrollment into future The MAH drug studies.

Even though children with ACH have the same intelligence as children without ACH, the complex musculoskeletal impairments increase the need for caregiver assistance during childhood. Children with ACH have a range of functional performance levels across self-care, mobility, and social cognition areas. These children require more physical assistance for everyday tasks, suggesting an increased burden of care for families (Ireland 2011; Ireland 2012).

Data collected using the WeeFIM, an instrument which measures functional performance across self-care, mobility, and social cognition showed that functional performance improved with age, however milestones were delayed across all ages in self-care and mobility compared with normative data (ie, subjects with ACH required greater caregiver assistance for longer for self-care and mobility than typically developing children without ACH; Msall 1994). Social cognition was similar to normative data. These findings are consistent with a population of ACH subjects (Ireland 2011).

In addition to physical impairments, there is evidence that height has an impact on HRQoL in children and adolescents with short stature (Abe 2009; Bullinger 2015). The PedsQL is a clinical outcomes assessment tool to measure HRQoL in children and adolescents. In this study, both children with ACH and their parents/caregivers generally rated the children's quality of life lower compared with a population of average stature children (Varni 2007).

The exception to this 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 to

be similar to the population of average stature children. These findings are consistent with a recent study in a population of ACH subjects (Witt 2019).

Data from the QoLISSY, a disease specific patient-reported outcome tool designed for short statured youth, showed that for the physical, social, and emotional domains, values were similar across ages. Of all five subject-rated domains (physical, social, emotional, coping, and belief), coping scored the lowest. However, coping and belief scores tended to increase for subjects 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. These findings are generally consistent with a recent study in a small population of ACH subjects (Lorne 2020). Data is also available in short stature subjects due to idiopathic short stature and growth hormone deficiency (Bullinger 2015); domain scores reported appear similar to those in 111-901.

In addition to the short stature and disproportionate growth that cause considerable functional limitation and impact on activities of daily living, numerous medical complications are associated with ACH. The comorbidities and burden of illness reported in this study (as medical history and AEs on study) are consistent with published literature (Fredwall 2019; Ireland 2014; Horton 2007; Hoover-Fong 2021). These complications include ear, nose and throat complications, sleep apnoea, chronic pain often caused by limb and spine deformities (including stenosis and kyphosis), and neurological complications such as cervical cord compression at the cervicomedullary junction and foramen magnum. The ear, nose and throat complications include persistent or recurrent otitis media accompanied by ear infections, hearing impairment, and enlargement of the tonsils and adenoids. The burden of illness is high with a frequent need for adenotonsillectomy, insertion of ventilation tubes, and spinal decompression.

Obesity is common in individuals with ACH and is recognized as contributing to common medical problems for this group of patients, including obstructive sleep apnea and limb and spine deformities (eg, genu varus, spinal stenosis). In this study and consistent with those reported in the literature in ACH (Hoover-Fong 2008, Hoover-Fong 2021), BMI Z-scores in ACH subjects were higher than in average stature children.

Vitamin D deficiency was a common finding in medical history, and approximately one quarter of subjects had AEs of low vitamin D on the study and initiated concomitant vitamin D. The range of vitamin D values was wide within all age groups. Median vitamin D levels remained within the normal range up to approximately 4 years of age. Thereafter, levels remained either at or below the lower limit of normal. Interpretation of these data from 111-901 is limited by the lack of published ACH-specific vitamin D data available for comparison.

In this study, blood pressure (SBP and DBP) trended towards the hypertensive range for subjects aged up to 4 years compared with sex-, age- and height-matched normative data (Flynn 2017). For subjects aged over 4 years, SBP was within the elevated blood pressure range and DBP was considered normal. One possible explanation could be underlying conditions such as obstructive sleep apnoea that can be associated with increase in blood pressure. Interpretation of this blood pressure data from 111-901 is limited by the lack of published ACH-specific blood pressure data available for comparison. The accuracy of measurement of blood pressure in ACH has been questioned, owing to challenges related to cuff size and cuff placement on rhizomelic shortened arms. Recent paper reported that hypertension is observed in 42% of adults with ACH and could be possibly related to increased BMI (Hoover-Fong 2021) however, it has been hypothesized that increased concentrations of endogenous CNP may negatively impact vascular health, which is of relevance specifically in ACH (Hoover-Fong 2019). Heart rate was within the normal range across age groups and trended lower as age increased, consistent with what is observed in the pediatric population (Fleming 2011).

CXM concentrations in pediatric subjects with ACH were relatively higher in the first two years of life (when growth rates are the fastest) with pronounced variability. CXM concentrations then stay relatively consistent across 3 to 12 years of age with a slight elevation between 8 and 11 years of age followed by a marked decrease after the age of 13 years, albeit observed with smaller sample sizes.

Data collected in 111-901 in 363 pediatric subjects with ACH demonstrate that subjects enrolled in this study closely resemble those of similar ages reported in published studies of children with ACH, with lower AGV than children without ACH, disproportionate short stature across all ages, and showing comorbidities consistent with the condition. While individuals with ACH appear to have cognitive and emotional functioning within the normal range, they require greater caregiver assistance (ie, self-care and mobility assistance) for a longer period of time than typically developing children without ACH. Generally, subjects were found to report lower HRQoL than average-statured reference groups. Overall, 111-901 subjects who later enrolled in subsequent MAH drug studies are similar to those who remained in 111-901 in relation to anthropometric measures and comorbidities consistent with the condition; data in both groups of subjects are consistent with published data reported in similar aged populations with ACH.

3. CHMP overall conclusion and recommendation

This stand-alone Post-Authorisation Measure (PAM) is being submitted to provide the EMA the final CSR for BMN111-901.

Study 111-901 was a multicentre, multinational **observational study** to **prospectively collect baseline growth measurements and adverse events in paediatric subjects with ACH** being considered for subsequent enrolment in future interventional studies with vosoritide, sponsored by the MAH.

No specific treatment was administered.

Overall, data collected in 111-901 in 363 pediatric subjects with ACH demonstrate that subjects enrolled in this study closely resemble those of similar ages reported in published studies of children with ACH, with lower AGV than children without ACH, disproportionate short stature across all ages, and showing comorbidities consistent with the condition.

Although the trial was impacted by the COVID-19 pandemic (missing scheduled visits in could not be Moreover, the trial seems to be a important reliable data source regarding the outcome of PRO data in the ACH population. While individuals with ACH appear to have cognitive and emotional functioning within the normal range, they require greater caregiver assistance (ie, self-care and mobility assistance) for a longer period of time than typically developing children without ACH. Generally, subjects were found to report lower HRQoL than average-statured reference groups. Overall, 111-901 subjects who later enrolled in subsequent studies are similar to those who remained in 111-901 in relation to anthropometric measures and comorbidities consistent with the condition; data in both groups are consistent with published data reported in similar aged populations with ACH.

There were no risks and no anticipated benefits to subjects participating in the study; however, subjects with at least 6 months of growth data were considered for possible participation in drug-treatment studies sponsored by the MAH (eligible subjects aged 0 to < 3 months at study entry were considered for participation in a The MAH-sponsored drug-treatment study with a minimum of 3 months of data).

No further questions as RSI are raised from assessment of the final CSR.

No changes in the product information or the RMS are applied or necessary in the Rapporteur's view.

No changes in the EPAR or regulatory actions are required in the Rapporteur's view.

No regulatory action required.

4. References:

- Hoover-Fong JE, Schulze KJ, McGready J, Barnes H, Scott CI. Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height. Am J Clin Nutr 2008;88(2):364-371.
- Hoover-Fong J, McGready J, Schulze K, Alade A, Scott C. A height-for-age growth reference for children with achondroplasia: expanded applications and comparison with original reference data. Am J Med Genet A 2017;173(5):1226-1230.
- Hoover-Fong J, Alade AY, Ain M, et al. Blood pressure in adults with short stature skeletal dysplasia. Am J Med Genet A 2020;182(1):150-161.
- Hoover-Fong J, Cheung MS, Fano V, et al. Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history. Bone. 2021;146:115872.
- Merker A, Neumeyer L, Hertel NT, et al. Growth in achondroplasia: Development of height, weight, head circumference, and body mass index in a European cohort. Am J Med Genet A 2018;176(8):1723-1734.