Official Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months

NCT Number: NCT03583697

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 02February2022

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Statistical Analysis Plan

Study 111-206

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Vosoritide in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months

Version 1.1: Final CSR

Date: 17 November 2021

1 SAP SYNOPSIS

TITLES OF STUDY: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of vosoritide in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months.
PROTOCOL NUMBER: 111-206
STUDY SITES: Approximately 10-15 clinical centers worldwide
PHASE OF DEVELOPMENT: Phase 2
OBJECTIVES: The primary objectives of the study are to: • Evaluate the safety and tolerability of vosoritide in children age 0 to < 60 months with Achondroplasia (ACH) • Evaluate the effect of vosoritide on change from baseline in standing height/body length Z-score The secondary objectives of the study are to: • Evaluate the effect of vosoritide on change from baseline in standing height/body length, annualized growth velocity (AGV), and upper: lower segment body ratio throughout the 52-weeks of the study • Evaluate the effect of vosoritide on other growth parameters and body proportions • Evaluate the effect of vosoritide on bone morphology/quality by X-ray and dual X-ray absorptiometry (DXA) • Evaluate the Pharmacokinetics (PK) of vosoritide in children age 0 to < 60 months with ACH • Evaluate hip function • Evaluate for hip, thigh, or knee pain, or change in gait • Evaluate the effect of vosoritide on health-related quality of life (HRQoL), developmental status, and functional independence using age-specific QoL and functional independence questionnaires (Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III], Activity of Daily Living and Functional Independence Measure (Wee-FIM), Infant Toddler Quality of Life Questionnaire (ITQOL), Child Behavior Checklist (CBCL) • Evaluate immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures • Evaluate the effect of vosoritide on bone metabolism and vosoritide pharmacodynamic (PD) biomarkers • Evaluate the effect of vosoritide on sleep apnea • Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions

- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

The exploratory objectives of the study are to:

- Document physical and phenotypic changes with clinical photography (optional)
- Evaluate genomic biomarkers (optional).

The exploratory objectives of the study are optional and will not be addressed in this SAP.

STUDY DESIGN AND PLAN: Study 111-206 is a phase 2 randomized, double-blind, placebo-controlled clinical trial of vosoritide in infants and younger children with a diagnosis of ACH.

Approximately 70 Subjects will be enrolled into 3 age cohorts: n ≥ 30 total for aged ≥ 24 to < 60 months, n ≥ 20 total for aged ≥ 6 to < 24 months, and n ≥ 20 total for aged 0 to < 6 months. There will be 3 sentinel subjects for each cohort, and the rest of subjects will be randomized 1:1 to treatment or placebo control and stratified by age for Cohorts 1 and 2.

All subjects who complete the 111-206 study will be eligible to receive vosoritide in the extension study 111-208 after the Week 52 visit.

ANALYSIS POPULATIONS:

The Full Analysis Set (FAS) is defined according to the intent-to-treat principle and includes all enrolled sentinel and randomized subjects with a signed informed consent.

The Per-Protocol (PP) population is defined as a subset of the FAS population who completed the treatment originally allocated (i.e., always received the assigned treatment), with a standing height/body length assessment at Week 52 following the protocol window, and with treatment compliance of at least 80%.

The Safety Population is a subset of the FAS who receive at least one dose of vosoritide or placebo in this study.

The PK Population is defined as all sentinel subjects and subjects randomized to vosoritide treatment group, who received at least one dose of vosoritide in this study and have at least one evaluable PK concentration.

The Immunogenicity Population is defined as all subjects in the Safety Population who have at least one evaluable immunogenicity sample.

STUDY ENDPOINTS AND ANALYSES:

Efficacy endpoints and analysis:

The primary efficacy endpoint is change from baseline in standing height/body-length Z-score at Week 52.

The key secondary efficacy endpoints include change from baseline at Week 52 in standing height/body length, AGV, and upper to lower body ratio. Other secondary efficacy endpoints include biomarker samples to evaluate the effect of vosoritide on bone metabolism, vosoritide pharmacodynamic biomarkers, growth parameters and body proportions, sleep apnea, skull and brain morphology, and clinical outcome assessments (developmental/functional/HRQoL status).

In addition to the summary statistics analyses for efficacy endpoints, model-based analysis will be conducted for change from baseline at Week 52 in standing height/body length Z-Score, standing height/body length, AGV, and upper to lower body ratio for all cohorts overall and/or by cohort, as appropriate.

Safety endpoints and analyses:

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 and presented by System Organ Class (SOC) and Preferred Term (PT). Summaries of AE's will include all AE's, serious adverse events (SAEs) and events of interest (EOI).

Clinical laboratory tests will be summarized descriptively. Shift tables tabulating Common Terminology Criteria for Adverse Events (CTCAE) severity grade at baseline versus worst post-baseline grade will be provided.

Vital signs will be summarized descriptively. Shift tables tabulating shifts from pre-dose (diastolic blood pressure (BP) < 40 mmHg, diastolic BP ≥ 40mmHg) to lowest post-injection value (diastolic BP ≥40mmHg) will be provided. Additional shift tables will describe similar pre/post injection shifts in vital signs.

X-rays and DXA will be performed on the extremities and spine to evaluate changes in bone morphology and quality.

Anti-vosoritide immunogenicity assessments will be summarized descriptively. Behavioral assessments with the CBCL will be summarized descriptively.

Other analyses:

Additional analyses will be conducted as appropriate to evaluate the impact of the COVID-19 pandemic on the study conduct.

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2 APPROVAL (SIGNATURE AND DATE)

DocuSigned by:
PI

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Clinical Science Lead
PI | DD MON YYYY

Pharmacovigilance Lead
PI | DD MON YYYY

DocuSigned by:
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Head of Statistical Scienc | DD MON YYYY

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
µg/kg	microgram/kilogram
ACH	achondroplasia
ADA	anti-drug antibody
AE	adverse event
AGV	annualized growth velocity
ANCOVA	Analysis of covariance
ANP	atrial natriuretic peptide
ATC	Anatomical Therapeutic Chemical
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BMN	BioMarin
BNP	brain natriuretic peptide
BP	blood pressure
BSAP	bone-specific alkaline phosphatase
CBCL	Child Behavior Checklist
CDC	Centers for Disease Control and Prevention
CM	concomitant medication
CRF	case report form
cGMP	cyclic guanosine monophosphate
CNP	C-type natriuretic peptide
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (v4.03)
CTX-II	C-terminal telopeptide of cross-linked collagen type II
DBL	database lock
DMC	data monitoring committee
DXA	dual x-ray absorptiometry
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
JNDA	Japan New Drug Application

HPA	hypothalamic pituitary adrenal
HRQoL	health-related quality of life
ISR	injection site reaction
ITQoL	Infant Toddler Quality of Life Questionnaire
IXRS	interactive web or voice response system
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCI	National Cancer Institute
NDA	New Drug Application
PD	pharmacodynamic
PK	pharmacokinetic
PP	per protocol
PT	preferred term
QTc-F	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SCFE	slipped capital femoral epiphysis
SD	standard deviation
SDS	standard deviation score
SE	standard error
SMQ	Standardized MedDRA query
SOC	system organ class
TAb	total anti-drug antibody
TEAE	treatment-emergent adverse event
TLGs	tables, listings, and graphs
WeeFIM	Activity of Daily Living and Functional Independence Measure
WHO	World Health Organization

4 INTRODUCTION

Study 111-206 (original protocol effective date: 06 December 2017) is a Phase 2 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of vosoritide in infants and young children with ACH, aged 0 to < 60 months.

This final SAP is based on Amendment 2 of Study 111-206 (date: 08 February 2019). It describes the analyses and evaluations that will be provided for the final clinical study report (CSR).

Where there are major differences between the protocol-defined analyses, and the SAP-defined analyses, these will be identified in the SAP. The SAP-defined analyses prevail.

4.1 Objectives of Study

The primary objectives of study are to:

- Evaluate the safety and tolerability of vosoritide in children age 0 to < 60 months with ACH
- Evaluate the effect of vosoritide on change from baseline in standing height/body length Z-score (height Z-Score may be used interchangeable)

The secondary objectives of study are to:

- Evaluate the effect of vosoritide on change from baseline in standing height/body length, AGV, and upper: lower body segment ratio throughout the 52 weeks of the study
- Evaluate the effect of vosoritide on other growth parameters and body proportions
- Evaluate the effect of vosoritide on bone morphology/quality by x-ray and DXA
- Evaluate the PK of vosoritide in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of vosoritide on HRQoL, developmental status, and/functional independence using age-specific QoL and functional independence questionnaires/QOL status (Bayley-III), Wee-FIM, ITQOL, and CBCL
- Evaluate immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of vosoritide on bone metabolism and vosoritide PD biomarkers
- Evaluate the effect of vosoritide on sleep apnea

- Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

The exploratory objectives are to:

- Documental physical and phenotypic changes with clinical photography (optional)
- Evaluate genomic biomarkers (optional)

The exploratory objectives of the study are optional and will not be addressed in this SAP.

4.2 Study Design

Study 111-206 is a phase 2 stratified randomized, double-blind, placebo-controlled clinical trial of vosoritide in infants and younger children with a diagnosis of ACH.

Subjects aged ≥ 6 months to < 60 months old who have documented ACH confirmed by genetic testing; at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry; and who meet the study eligibility criteria, will participate. Eligible subjects ranging from 0 months to < 3 months old may enroll directly into 111-206 and have a minimum of 3 months of pre-treatment observation prior to commencing treatment with investigational product or may enroll in 111-901 for a minimum of 3 months of pretreatment growth assessment immediately before roll-over to 111-206.

Approximately 70 subjects will be enrolled at approximately 10-15 clinical centers worldwide.

Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive vosoritide, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 months to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive vosoritide, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)

- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who receive vosoritide, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

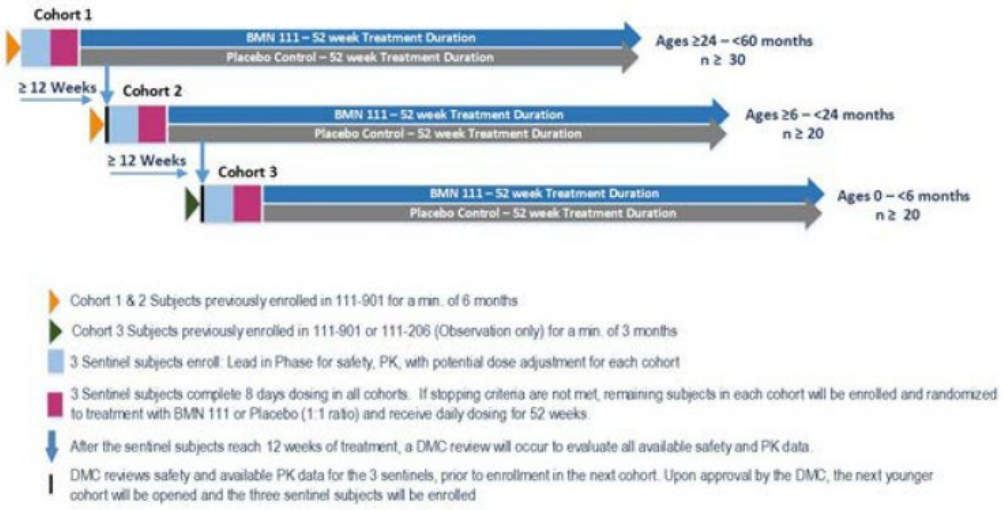
Sentinel subjects from each cohort will be enrolled, treated with vosoritide, and studied for short-term safety and PK data. After the sentinel data are evaluated within a cohort additional recruited subjects will be randomized to receive vosoritide or placebo subcutaneous daily (1:1 ratio) for 52 weeks.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age as follows:

All sentinel and randomized subjects in Cohort 1 received 15 µg/kg dose. Sentinel subjects in Cohort 2 initially received 15 µg/kg dose and the dose was escalated to 30 µg/kg while they remained < 24 months of age following review of PK data as per protocol. All randomized subjects in Cohort 2 will receive 30 µg/kg dose while they remained < 24 months of age. All sentinel and randomized subjects in Cohort 3 received 30 µg/kg dose while they remained < 24 months of age. The dose for all sentinel and randomized subjects in Cohorts 2 and 3 will be adjusted to 15 µg/kg/day after they turn 24 months old.

The 111-206 study design is presented in Figure 4.2.1. All subjects who complete the 111-206 study will be eligible to receive vosoritide in the extension study 111-208 after the Week 52 visit.

Figure 4.2.1: Study Design



4.3 Study Populations

Subjects aged 0 to < 60 months old, with documented ACH confirmed by genetic testing, and who meet the study eligibility criteria will participate.

For additional criteria for selection of study population, please refer to inclusion and exclusion criteria for the protocol.

4.4 Study Dosage and Administration

In Study 111-206, sentinel subjects in Cohort 1 will receive an initial daily dose of 15 µg/kg. All available safety and PK data will be reviewed after 3 sentinel subjects reach Day 8. If the criteria for dose adjustment are met, the 3 sentinel subjects will be started on the new adjusted dose at their next scheduled visit and the remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. The 3 sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment. Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

4.5 Sample Size Determination

Approximately 70 subjects aged 0 to < 60 months at study entry will participate in 111-206. No formal sample size calculations were performed. The number of subjects is considered appropriate to evaluate the safety and efficacy of vosoritide in the target population.

4.6 Blinding and Randomization Methods

4.6.1 Blinding Method

This is a placebo-controlled, double-blind study. Blinding is strictly maintained during the study and a study specific masking plan describes how potentially unblinding data are handled during the lifetime of the study. The study will remain blinded until after all data has been entered, and the final database has been locked.

4.6.2 Randomization Method

The centralized randomization with stratification is managed by an external vendor, using IXRS technology.

Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. In each cohort, eligible subjects will be randomized in a 1:1 ratio to vosoritide or placebo after 3 sentinel subjects are treated. Cohorts 1 and 2 will be stratified by age. Subjects are randomized separately within each cohort in Japan.

4.7 Interim Analysis

No formal interim futility/efficacy analyses are planned. Two informal interim analyses including data from both Studies 111-206 and 111-208 were performed for selected domains: one for New Drug Application (NDA) to Food and Drug Administration (FDA) and marketing authorization applications (MAA) to European Medicines Agency (EMA), dated 18December 2019, and another for Japan New Drug Application (JNDA), dated 11November 2020. For these analyses, subjects remained blinded and no efficacy data was analyzed for the randomized subjects nor post baseline listings except for serious adverse events.

In addition to safety and PK monitoring by BioMarin Personnel, an independent data monitoring committee (DMC) will act in an advisory capacity to BioMarin to monitor subject safety and PK of subjects who participate in the study. A DMC review will occur to evaluate all available safety and PK data after the sentinel subjects complete 12 weeks of dosing, and DMC will make recommendations for stopping or continuing the study, and endorse dose adjustments if needed, based on pre-specified criteria. DMC data review meetings occur approximately every 6 months during the course of the study.

5 GENERAL ANALYSIS CONSIDERATIONS

The analyses described in this final SAP are based on Amendment 2 of the protocol (date: 08 February 2019).

Individual subject data that is reflected in data summaries will be provided in listings. Unless otherwise specified, all listings will be by cohort, by sentinel/randomized subjects, by treatment group, and ordered by subject number, where subject number includes the site number.

Unless otherwise specified, summary tables for efficacy variables will use format in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively. Summary tables for safety variables will be separated by cohort and overall by treatment group using format in Table 5.4.

Table 5.1: Format for Efficacy Summary Analyses for Cohort 1

Sentinel	Randomized						All Vosoritide Treated*		
	Vosoritide			Placebo					
	≥ 24 to < 36 months	≥ 36 to < 60 months	Overall	≥ 24 to < 36 months	≥ 36 to < 60 months	Overall	≥ 24 to < 36 months	≥ 36 to < 60 months	Overall

*All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Table 5.2: Format for Efficacy Summary Analyses for Cohort 2

Sentinel	Randomized						All Vosoritide Treated*		
	Vosoritide			Placebo					
	≥ 6 to < 15 months	≥ 15 to < 24 months	Overall	≥ 6 to < 15 months	≥ 15 to < 24 months	Overall	≥ 6 to < 15 months	≥ 15 to < 24 months	Overall

*All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Table 5.3: Format for Efficacy Summary Analyses for Cohort 3

Sentinel	Randomized		All Vosoritide Treated*
	Vosoritide	Placebo	

*All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Table 5.4: Format for Safety Summary Analyses for Cohort 1*

Sentinel	Randomized		All Vosoritide Treated**
	Vosoritide	Placebo	

* Cohort 2, Cohort 3, and Overall will have the same format as Cohort 1.

**All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Baseline growth measures (other than AGV, baseline AGV is defined in Section 14.3.2) and baseline weight are those assessed on Day 1 of dosing, regardless of timing relative to dosing. (Note: If no assessments are available, then the baseline assessment will be the last non-missing assessment prior to Day 1). Baseline assessments are the last non-missing on-study assessments prior to administration of study treatment. Change from baseline is calculated as: (post-baseline value – baseline value); Percent change from baseline is calculated as: ([post-baseline value – baseline value]/baseline value) x100.

The screening visit will not be presented in descriptive summaries over time. When the analysis windows have been applied (see Section 5.4), data collected at the screening visit may be included in the baseline assessment. All assessments will be listed, but only those assessments assigned to visits according to the windows applied (see Section 5.4) will be summarized in tables or graphically. Exceptions to this are summaries of the worst post-baseline laboratory data in shift tables where all assessments are considered.

Unless otherwise specified, summary statistics n, mean, standard deviation (SD), median, 25th and 75th percentile, minimum, and maximum will be provided for numerical variables. The mean, 25th percentile, median, 75th percentile, and estimates of precision (e.g. SD, confidence interval) will be displayed to one more decimal place than the collected data. Minimum and maximum values will be presented to the same decimal places as the collected data. The number of decimal places to which endpoints are reported follow the project programming standards.

Number and percentage will be provided for categorical variables. When summarizing categorical data, for mutually exclusive categories, the sum of the individual categories, including a separate “Missing” category, should equal 100%. Unless otherwise specified, if categories have no data, then they will not be displayed.

All statistical analyses will be performed using SAS® version 9.4 or a later release (SAS Institute, North Carolina, USA) and results be presented in the form of tables, listings, and graphs (TLGs). All statistical analyses, including dataset creation and output generation, will

be performed by Biostatistics and Statistical Programming personnel of BioMarin's Biometrics department.

5.1 Analysis Populations

5.1.1 Full Analysis Set

The Full Analysis Set (FAS) is defined according to the intent-to-treat principle and includes all enrolled sentinel and randomized subjects with a signed informed consent. The FAS will be the main analysis population for summaries and/or analyses described in the SAP, including but not limited to summaries and/or analyses of demographics, baseline characteristics, dispositions, and all efficacy endpoints.

All listings, excluding screen failures, will be produced on the FAS.

5.1.2 Per-Protocol

The Per-Protocol (PP) population is defined as a subset of the FAS population who completed the treatment originally allocated (i.e., always received the assigned treatment (vosoritide or placebo)), with a standing height/body length assessment at Week 52 following protocol window, and with treatment compliance of at least 80%.

The PP population will be used for sensitivity analysis of the primary and key secondary efficacy endpoints only.

5.1.3 Safety

The Safety Population is a subset of the FAS who receive at least one dose of vosoritide or placebo in the study. The Safety Population will be used to present the safety summaries by actual treatment received. Subjects randomized to one treatment group, who only receive the study treatment for the other treatment group, will be analyzed in the arm of the study treatment they received.

The Safety Population will be used to present the safety data.

5.1.4 PK

The PK Population is defined as all sentinel subjects and subjects randomized to vosoritide treatment group, who received at least one dose of vosoritide in this study and have at least one evaluable PK concentration.

5.1.5 Immunogenicity

The Immunogenicity Population is defined as all subjects in the Safety Population who have at least one evaluable immunogenicity sample. Subjects randomized to one treatment group, who only receive the study treatment for the other treatment group, will be analyzed in the arm of the study treatment they received.

5.2 Pooling of Data from Sites with Small Enrollment

Not applicable, as there are no analyses by site.

5.3 Study Day Derivation

Study day in 111-206 will be determined by subtracting the initial study treatment start date from a visit date plus 1 if the visit date occurs on or after the initial study treatment start date. Otherwise, the study day will be the visit date minus the initial study treatment start date. Therefore, Study Day 1 will occur on the initial study treatment start date. i.e.

- Study Day 1 = Day of first dose of study treatment.
- If Visit Date < Study Treatment Start Date, then Study Day = Visit Date - Study Treatment Start Date
- If Visit Date >= Study Treatment Start Date, then Study Day = Visit Date - Study Treatment Start Date +1

5.4 Visit Windows for Analysis

An assessment for a subject will be classified according to the study day of the assessment where it falls within a window.

Observational data in 111-901 for subjects who enrolled in 111-206 and are included in the corresponding analysis population will be used in efficacy summary tables and figures. For Cohort 3 subjects, data from the observational period in 111-901 or 111-206 will be included. The analysis visits and windows for observational assessments in 111-901 and 111-206 are defined in Table 5.4.1. Unless otherwise specified, only the derived visits listed in the table will be included in summary tables and figures.

Table 5.4.1: Visit Windows for Observed Assessments in BMN 111-901 and BMN 111-206

Derived Visit	Target Day[a]	Analysis Window[a]
≥ 3 Months Prior in 111-206 or 111-901 for Cohort 3 subjects*	-91	target day +/- 42 days
≥ 6 Months Prior in 111-901*	-182	target day +/- 42 days

[a] Target days and analysis windows are relative to the 111-206 Day 1 date defined in Section 5.3 above.

[*] In the event a subject does not have an assessment in the 3 months prior or 6 months prior window then the closest assessment to the target date will be considered. If the two closest assessments to the target day are equidistant from the target day, the latest assessment will be used.

For each subject and growth measure in study 111-901, the record closest to the target day within the analysis window will be retained for inclusion in summary tables.

Spaghetti plots of standing height/body length Z-score will include measures every 6 months recorded and including the "≥ 6 months prior", "≥ 3 months prior" for subjects in Cohort 3 from Study 111-901 or 111-206. This will allow for all subjects with height assessments ≥ 3 months prior to Day 1 to have at least one assessment included.

The analysis windows for assessments in 111-206 are defined in Table 5.4.2. The analysis windows are designated to be consecutive for scheduled visits to accommodate delayed visits due to impact of COVID-19. The upper bound of each visit window will be target day plus half of the difference between the current target day and the next target day, and the lower bounds of the window will be the upper bound of the previous window plus 1 except for Day 1, Day 2, Day 3, and Week 52. Lower bound, upper bound, and target date are the same for Day 1, Day 2, and Day 3. The upper bound of Week 52 will be target day plus 42 days. If there are two or more assessments within a designated window, the assessment that is closest to the target day will be used for analyses. If the two closest assessments to the target day are equidistant from the target day, the assessments taken on a scheduled visit per case report form (CRF) page will be used; if both are scheduled visits but not on the same day, the latest assessments will be used; if both are on the same day, the average of the assessments will be used. Unless otherwise specified, all analyses are based on derived visits.

Table 5.4.2: Visit Windows for Observed Assessments in 111-206

Derived Visit	Target Day[a]	Analysis Window[a]
Baseline		The last assessment prior to the first dose of study treatment unless otherwise specified.
Day 1	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 8	Day 8	Day 4 - 15
Week 3	Day 22	Day 16 - 33
Week 6	Day 43	Day 34 - 68
Week 13	Day 92	Day 69 -117
Week 20	Day 141	Day 118 - 162
Week 26	Day 183	Day 163 - 229
Week 39	Day 274	Day 230 - 320
Week 52	Day 365	Day 321 - 407

[a] Target days and analysis windows are relative to Day 1 date defined in Section 5.3.

5.5 Handling of Dropouts and Missing Data

For descriptive summaries, missing data will not be imputed. For model-based analyses, an imputation will be conducted for endpoints missed at Week 52. Detailed imputation rules are described in Section 14.1.

Other than for partial/missing dates described below, there will be no imputation for safety data.

5.5.1 Partial Dates

Where start and stop dates for medications or adverse events are incomplete, imputation rules will be applied.

In the event that the start date of a medication/AE is partial, the following imputation rules will be applied:

- If only day is missing, then the start date will be imputed as the first day of the month. If month and year are the same as the month and year of first dose of study treatment, then the start date will be imputed as the first dose date in the study in which the AE occurred.

- If only year is non-missing, then the start date will be imputed as the first day of the year. If year is the same as the year of first dose of study treatment, then the start date will be imputed as the first dose date in the study in which the AE occurred.

In the event that the stop date of a medication/AE is partial, the following imputation rules will be applied:

- If only day is missing, then the end date will be imputed as the last day of the month.
- If only year is non-missing, then the end date will be imputed as the last day of the year. If the imputed date is beyond the study completed or discontinued date of the study in which the AE occurred, the imputed date will be replaced with the study completed or discontinued date.

6 SUBJECT DISPOSITION

Disposition will be presented based on the FAS. The number of subjects enrolled/randomized, the number of subjects who received study treatment, the number of subjects who completed study treatment, and the number of subjects who completed the study will be reported separately by cohort and overall by treatment group using format as specified in Table 5.4.

Disposition data will be listed for both the sentinels and randomized subjects by cohort and treatment group, and will indicate the investigator site. In addition, a listing will be provided for those subjects who were screen failures, along with the reason for screen failure.

7 DISCONTINUATION AND COMPLETION

For subjects who prematurely discontinued from the study, the primary reason for discontinuation will be summarized. A similar summary will be provided for subjects who discontinued study treatment.

The number of subjects who completed study treatment and the number of subjects who completed the study will be summarized by cohort and overall by treatment group using format as specified in Table 5.4. All summaries will be based on the FAS.

Listing will be provided on the FAS.

8 PROTOCOL EXEMPTIONS AND DEVIATIONS

The number and percentage of subjects with any protocol deviation, any major protocol deviation, and any minor protocol deviation will be presented separately by cohort and overall by treatment group using format as specified in Table 5.4, according to the categories described in the study specific protocol deviation plan. Reasons for major/minor deviations will be summarized. Subjects who received the wrong treatment will be identified after data base lock and considered as a Major Protocol Deviation.

All summaries will be based on the FAS.

All protocol deviations will be listed for sentinel and randomized subjects by cohort. sentinel/randomized subjects, treatment group, and subject ID. A separate listing of all major deviations which have been classified as a “Dosing Irregularity” will also be provided.

In addition, a summary and listing of COVID-19 specific protocol deviations will be provided.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for the FAS, and presented for by cohort by treatment group with the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively and Table 5.4 for Overall. Rules on standing height/body length and sitting height/crown to rump length are provided in Section 14.1.

Demographics will be summarized as:

- Age at Screening (months with 1 decimal place)
- Age at Day 1 (months with 1 decimal place)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian [Japanese/Other], Black or African American, Native Hawaiian or Pacific Islander, White, Multiple, Not Provided Due to Patient Privacy Rules)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Baseline characteristics will be summarized as:

- Weight (kg) and Weight Z-score
- Body Mass Index (BMI) (kg/m^2), and also BMI Z-score for subjects aged 24 months or older

Baseline growth measures will be summarized as:

- Height Z-Score (Refer to Section 14.2.1)
- AGV (cm/yr)
- Standing Height/Body Length (cm)
- Sitting Height/Crown to Rump(cm)
- Lower Body Length (cm) = Standing Height - Sitting Height
- Head Circumference (cm)
- Upper Arm Length (cm)
- Lower Arm (Forearm) Length (cm)
- Arm Span (cm)
- Upper Leg Length (Thigh) (cm)
- Knee to Foot Height (cm)

- Tibial Length (cm)
- Upper to Lower Body Segment Ratio
- Arm Span to Standing Height Ratio
- Upper Arm Length to Lower Arm (Forearm) Length Ratio
- Upper Leg Length to Tibial Length Ratio

A listing of each sentinel and randomized subject's demographic/baseline data will be provided.

10 MEDICAL HISTORY

Medical history will be solicited from each subject, including all major illnesses, diagnoses, and surgeries that the subject has ever had; any prior or existing medical conditions that might interfere with study participation or safety; and evaluation for knee, thigh, hip or groin pain, or change in gait/activity.

All medical history terms will be coded in accordance with MedDRA Version 24.1 that each term is assigned a SOC and PT.

A list of PTs considered to be ACH-related will be reviewed prior to the data cut. A listing for the complete list of final terms will be generated, retained in the study file, and documented in the CSR.

All recorded medical history will be summarized on the FAS by SOC and by PT by cohort and overall by treatment group using format as specified in Table 5.4, ordered by descending order of frequency of SOC in the overall population. In addition, achondroplasia-related medical history will be listed and summarized separately by SOC and PT in a similar manner.

The number of subjects with abnormal physical exam results at screening will be summarized and listed.

A listing of each subject's medical history will be provided, plus a listing of each subject's achondroplasia-related medical history.

11 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be summarized for the FAS. For analysis purposes, the following definitions will be used to determine prior and concomitant medications for the entire study period:

- Prior medications: Any medications taken and ended prior to the initial study treatment administration date will be considered prior medications.
- Concomitant medications: Any medications taken on or after the initial study treatment administration date up to 30 days after discontinuation of study treatment will be considered concomitant medications and included in summary tables. This also includes medications initially taken prior to the initial study treatment administration date but continued or ended on or after the initial study treatment administration date.

Concomitant medications will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4, and a separate summary will be provided which includes only those concomitant medications that were initiated on study.

All medications will be coded using the latest version available within BioMarin of the World Health Organization Drug (WHO Drug) dictionary (Version September 2021). Prior and concomitant medication use will be separately summarized by Anatomical Therapeutic Chemical (ATC) medication class (Level 2) and preferred name (i.e., generic medication name). If a medication doesn't have ATC level 2, they are grouped as "ATC Level 2 classification unavailable". A subject reporting the same medication more than once will be counted once when calculating the number and percentage of subjects who received that medication. A listing of prior and concomitant medications will be provided. In addition, a listing for COIVD vaccine will be provided.

12 COMPLIANCE

Treatment compliance will be calculated based on the study treatment preparation and study treatment administration records captured in the eCRF, and summarized separately by cohort and overall by treatment group using format as specified in Table 5.4 for the safety population.

For each subject it considers all data up to the last recorded dose. For each column, results will be separated for 15 µg/kg, 30 µg/kg, and overall.

For each daily injection, the amount of study treatment taken will be calculated based on the number of units in the syringe pre-injection, minus the number of units remaining in the syringe post-injection. For the cases that the number of units in the syringe pre-injection is not captured in the eCRF, if response to "Was study drug administrated?" is "Yes", then it will be assumed to be the same as the planned dose; if response to "Was study drug administrated?" is "No", then it will be assumed to be missing and these records will not be included in the compliance calculation.

The total amount of study treatment taken (µg) will be calculated based on the amount of study treatment taken (units) in the corresponding treatment duration by using the following formula:

dose of study treatment (µg) = unit of study treatment * vial concentration/ weight *10.

The total amount of study treatment planned (µg) is determined based on the duration of treatment and the planned dose per day, where dose will be calculated based on the planned unit per day by using the same formula as above.

Percentage compliance for each subject will be derived from the total amount of study treatment intake divided by the planned study treatment intake, and multiplied by 100:

$$\text{Treatment Compliance (\%)} = \frac{Total\ Amount\ of\ Study\ Drug\ Taken\ (doses)}{Total\ Amount\ of\ Study\ Drug\ Planned\ (doses)} \text{ x } 100$$

Treatment compliance will be calculated and summarized separately by cohort and overall by treatment group using format as specified in Table 5.4. For each column, results will be separated for 15 µg/kg, 30 µg/kg, and overall.

- Compliance with protocol-specified treatment regimen (%)
- Compliance with protocol-specified treatment regimen (≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥100%, >=110%, >=120%)

Listings will be provided for compliance.

13 EXTENT OF EXPOSURE TO STUDY TREATMENT

Dosing information is recorded by subjects in the paper diary and also by the site on visit days. In the case of duplicate records with the same date, if the investigator confirms the date, then investigator reported dosing data will be used. All summaries will be produced based on the safety population, and presented separately by cohort and overall by treatment group using format as specified in Table 5.4. For each column, results will be separated for 15 µg/kg, 30 µg/kg, and overall.

Descriptive statistics will be provided for the following variables:

- Duration of treatment (days)

  = Date of last dose – Date of first dose + 1
- Total number of doses administered

  = Number of doses administered between date of Day 1 and date of last dose
- Total number of doses missed

  = Number of doses missed between date of Day 1 and date of last dose
- Total amount of weight adjusted dose administered (µg/kg) by planned dose
- Average weight-adjusted daily dose administered (µg/kg/day) by planned dose

The frequency and percent of subjects will be provided for the following variables, where missed doses are counted between the date of first dose (Day 1) and date of last dose:

- Number of subjects who missed at least one dose
- Number of subjects who missed more than one dose
- Number of subjects who missed more than 5 consecutive doses
- Number of subjects who missed more than 10 consecutive doses

The frequency and percent of events will be provided overall for the following variable:

- The total number of missed doses and reason for each missed dose (Site Error, Parent/Caregiver Error, Home Health Error, Adverse Event, Other, Missing) will be provided.

A listing of each subject's extent of exposure by planned dose 15 µg/kg and 30 µg/kg will also be provided.

14 EFFICACY EVALUATIONS

14.1 General Approaches for Analyzing Growth Parameters

All growth parameters assessed by anthropometric measurements are measured at Baseline, Day 1, Week 6, Week 13, Week 26, Week 39, Week 52, and early termination visit.

Growth parameters are measured 3 times for each assessment. It is the mean of these 3 assessments that are considered for the summaries and analyses. In the event that all 3 are not available, the mean of the 2, or the individual assessment is taken. All measures and means of the measures will be included in the listings.

The general rule when summarizing height (standing and sitting) is that standing height/sitting height will be used if subjects ≥ 24 months, body length/crown to rump will be used if subjects < 24 months. For subjects with both sets of measurements available, like to like will be used based on their measurements available for their age at baseline.

Thus, in general, for subjects in Cohort 1 standing height and sitting height will be summarized. For subjects in Cohorts 2 and 3 body length and crown to rump will be summarized. If body length is not measured and standing height is available, standing height will be used. If both sets of measures are available, like to like will be used based on their measurements available for their age at baseline.

These rules will impact the following growth endpoints: standing height/body length Z-Score, standing height/body length, AGV, sitting height/crown to rump, lower body length, arm span to height ratio, upper to lower body segment ratio, BMI, and BMI Z-score.

BMI and BMI Z-score will only be derived for subjects aged 24 months or older.

Body length and crown to rump will not be summarized separately but integrated within the summaries for standing height and sitting height. Body length and crown to rump are however provided separately in a listing.

Appendix 25.1 provides details of the derivations used for each endpoint.

All efficacy endpoints will be assessed using the FAS.

Visit windows are applied for all assessments (see Section 5.4) and are used to summarize the growth measures by visit.

All parameter assessments are considered for inclusion in analyses.

With the exception of AGV (see Section 14.3.2), summary tables for all growth measures including standing height/body length Z-score, standing height/body length, upper to lower body segment ratio, body proportion ratios, other growth measures (see Section 14.3.5), BMI, BMI Z-scores, and weight Z-scores will include assessments at baseline, Week 26 and Week 52 from Study 111-206, and 6 months prior in Study 111-901. For subjects in Cohort 3 assessments at 3 months prior to baseline in Studies 111-206 or 111-901 will be included.

Each table will include summaries of the absolute observed measures and its change from baseline at each of these time points. The tables will summarize data separately by cohort by treatment group using format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

ANCOVA models will be conducted for change from baseline at Week 52 in standing height/body length Z-Score, standing height/body length, AGV, and upper to lower body ratio for all cohorts overall and/or by cohort, as appropriate. Unless otherwise specified, all models will include the following baseline covariates: age at baseline, baseline AGV, and sex. Analyses of standing height/body length Z-Score, standing height/body length, and upper to lower body ratio will include their baseline as additional covariate.

For the model-based analyses, if the required assessment at Week 52 is missing but there are height assessments before and after Week 52, a linear interpolation using the measurements closest to the before and after Week 52 will be used, otherwise those with no assessment after Week 52 will be excluded from the primary analyses.

In addition to the primary analyses conducted on FAS, sensitivity analyses will also be conducted and are described in Section 14.2.

Results of the statistical analyses will be provided in separate tables, including the least-squares (LS) mean change from baseline at Week 52 for each treatment group, the treatment difference in LS means (calculated as vosoritide - Placebo), the 95% confidence interval (CI) for the treatment difference, and corresponding 2-sided p-value.

Listings for standing height/body length and standing height/body length z-score will include all assessments (i.e., all measures and means of the measures) and spaghetti plots for height and height Z-score will include assessments every 6 months and will be ordered by cohort, sentinel/randomized subject, treatment, subject ID and visit date including 111-901 and 111-206.

14.2 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in standing height/body length Z-score at Week 52.

Each measurement of derived standing height/body length will be converted to an age-and sex-appropriate standard deviation score (SDS), also referred to as a Z-score, by comparison with reference data available for average stature children from the CDC. Note no data conversions are applied between body length and standing height as recommended for average stature.

Standing height/body length Z-scores will be derived using CDC references and macro (CDC, 2019).

14.2.1 Primary Analyses

The standing height/body length Z-score at ≥ 6 Months Prior to baseline, ≥ 3 Months Prior to baseline for Cohort 3, baseline, Week 26 and Week 52, and it's change from baseline at Week 26 and Week 52 will be summarized and presented separately by cohort by treatment group using format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

A spaghetti plot of the height Z-score will be presented for each subject.

Height Z-scores derived for all visits from 111-901 and 111-206 will be included in data listings and height Z-scores derived for every 6 months (including 6-month prior and 3-month prior) will be included in the spaghetti plots.

For the model-based ANCOVA analyses, estimand formulation is as follows:

- Population: FAS
- Variable: Change from baseline in standing height/body length Z-Score at Week 52
- Intercurrent event: Regardless of whether or not switching to rescue medication had occurred or subjects had discontinued from the treatment. See Section 14.1 for handling of missing data
- Population-level summary: Lsmean difference and 95%CI between the treatment groups based on ANCOVA models defined in Section 14.1

ANCOVA model will include the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where baseline covariates include age at baseline, sex, baseline AGV, and baseline height Z-score. The following SAS Proc Mixed with option OBSMARGINS for lsmeans will be used to perform the analysis:

```
PROC MIXED;
CLASS Treatment Sex;
MODEL Change from baseline in height Z-Score at Week 52 = Treatment
Age_baseline Sex AGV_baseline Height Z-Score_baseline;
LSMEANS Treatment / DIFF CL OM;
ESTIMATE 'Active - Placebo' Treatment 1 -1/CL;
RUN;
```

The analysis will be repeated by also including sentinel subjects from the corresponding cohort.

14.2.2 Sensitivity Analyses

The following sensitivity analyses will be conducted on the primary efficacy endpoint:

(1) Summary statistics and model-based analyses on the subjects in the PP population

(2) Model-based analyses using a multiple imputation washout model to derive missing data at week 52 for subjects excluded from the primary analysis

14.3 Secondary Efficacy Endpoint(s)

14.3.1 Standing Height/Body Length

Rules for standing height/body length is described in Section 14.1.

The standing height/body length and its change from baseline will be summarized and presented separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

Standing height/body length will be analyzed using the same methods and estimand formulation as the primary efficacy endpoint analysis and sensitivity analyses. An analysis of change from baseline in standing height/body length at Week 52 will be performed using an ANCOVA model that includes the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where baseline covariates include age at baseline, sex, baseline AGV, and baseline standing height/body length.

Standing height/body length for all visits will be included in data listings including data from 111-901 and 111-206.

Spaghetti plots of standing height/body length at every 6 months assessments including height assessments collected in the 111-901 study (3-month prior for Subjects in Cohort 3)

will be provided for each subject separately by cohort. This plot will include age-sex specific reference ranges for average stature children (from CDC, 2019) and age-sex specific reference ranges for short stature children (Hoover-Fong, 2008).

For these plots if only body length is used, it will be indicated in the plot.

14.3.2 Annualized Growth Velocity

For a given interval [Date1, Date2], the AGV is defined as follows:

AGV (cm/yr) = (Derived Standing Height at Date 2-Derived Standing Height at Date 1)/(Interval Length (Days)) x 365.25

where the interval length in days is calculated as Date2 - Date1.

AGV (cm/yr) will be calculated at baseline, Week 26, and Week 52. AGV at baseline will be calculated by using height measurements in Study 111-901 at least 6 months prior to Day 1 of Study 111-206 for subjects in Cohorts 1 and 2, and using height measures in Study 111-901 or 111-206 at least 3 months prior to Day 1 of Study 111-206 for subjects in Cohort 3. AGV at other time points will be calculated cumulatively from Day 1 of 111-206 and every 6 months interval.

The absolute values for cumulative AGV and 6-month AGV and their change from baseline will be summarized and presented separately by cohort by treatment group using the format specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

Cumulative AGV will be analyzed using the same methods and estimand formulation as the primary efficacy endpoint analysis and sensitivity analyses. An analysis of change from baseline in cumulative AGV at Week 52 will be performed using an ANCOVA that includes the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where baseline covariates include age at baseline, sex, and baseline AGV.

A box and whisker plot will be provided for AGV (cm/yr) over time by cohort and treatment group.

Listings and individual subject figures for the cumulative AGV and 6 months AGV will include AGV for all height assessments at all scheduled visits.

14.3.3 Upper to Lower Body Segment Ratio

The upper to lower body segment ratio will be calculated at each visit as follows:

Upper to Lower Body Segment Ratio = $\frac{Derived\ Sitting\ height(cm)}{Derived\ Standing\ height(cm) - derived\ Sitting\ height(cm)}$.

The ratio of derived sitting height and derived standing height will also be calculated.

The upper to lower body segment ratio, the sitting to standing height ratio, and their change from baseline will be summarized and presented separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

Upper to lower body segment ratio will be analyzed using the same methods and estimand formulation as the primary efficacy endpoint analysis and sensitivity analyses, an analysis of change from baseline in the upper to lower body segment ratio at Week 52 will be performed using an ANCOVA model that includes the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where baseline covariates include age at baseline, sex, baseline AGV, and baseline upper to lower body segment ratio.

Upper to lower body segment ratio and sitting to standing height ratio derived for all visits will be included in data listings including data from 111-901 and 111-206.

14.3.4 Body Proportion Ratios

Body proportion ratios include:

- Upper Arm Length to Lower Arm (Forearm) Length Ratio
- Upper Leg Length (Thigh) to Knee to Heel Length Ratio
- Upper Leg Length (Thigh) to Tibial Length Ratio
- Arm Span to Standing Height Ratio

The absolute values and its change from baseline will be summarized and presented separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

All assessments will be listed.

14.3.5 Other Growth Measures

Other growth measures include:

- Sitting Height (cm)/Crown to Rump (cm)
- Upper Leg Length (Thigh) (cm)
- Lower Leg Length: Knee to Foot (cm)

- Lower Leg Length: Tibia Length (cm)
- Head Circumference (cm)
- Upper Arm Length (cm)
- Lower Arm (Forearm) Length (cm)
- Arm Span (cm)

In addition, derived standing height and derived sitting height will be calculated as specified in Section 14.1, and a measure of lower body length will be calculated as follows:

- Lower Body Length (cm) = Derived Standing height – Derived Sitting height

Baseline growth measures are those assessed on Day 1, regardless of timing relative to dosing. All summaries and analyses will be based on the FAS.

For each of the above growth measures (including lower body length), the absolute values and its change from baseline will be summarized and presented by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

All assessments will be listed by subject and visit.

14.4 Health-Related Quality of Life

The Health-Related Quality of Life (HRQoL) questionnaires and functional independence questionnaires are captured at Baseline, Week 26, Week 52. All summaries will be generated on the FAS.

Each table will include summaries of the absolute measures at each of these time points and change from baseline at every 26 weeks. The tables will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

The statistical summaries will include the number of subjects with assessable data, mean, SD, median, 25th and 75th percentile, minimum and maximum. Subjects will not be included in a summary table if there is no baseline assessment available.

Separate summary tables will be provided for the total summary scores and the individual domains (scales). Individual questions (items) are not included in the summary tables.

Age-defined versions within the same questionnaire will be summarized together. If subjects progress during the course of the study from one age-defined questionnaire to the next age-

defined questionnaire the results will be summarized together and the baseline assessment from the child's first questionnaire is referred to when summarizing change from baseline.

If a questionnaire for the wrong age group was filled, outcomes will not be included in the summary table but will be included in the listings.

Self-reports and parent-reports will be summarized separately but together in the bat charts.

All subject data listings will include total scores, and domain (scale) scores.

14.4.1 Bayley-III

The Bayley-III is a performance-based outcome assessment for use in children from 1 to 42 months.

Scales include Cognitive scale, Language (Receptive Communication and Expressive Communication subscales) scale, and Motor (Gross and Fine Motor subscales) scales.

In addition to its use for subjects ranging from 1 to 42 months old, the Bayley-III assessment will be administered to those entering the study between 42 and 60 months old and for the remainder of the duration of this study, as this assessment can capture ongoing developmental issues associated with ACH. Bayley-III is waived for subjects < 1 month old.

Scales/Subscales:

- Cognitive
- Language
    - Receptive Communication
    - Expressive Communication
- Motor
    - Fine Motor
    - Gross Motor

Each (sub)scale yields a total raw score which is then standardized according to the subject's chronological age (scaled scores).

Scoring

Number of items depends on which set is given in each domain. The number of questions administered depends in part on the child's age and on their developmental level.

The total raw scores for the Cognitive Scale and the Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor subscale are the sums of the number of points earned for a (sub)scale.

The raw scores cannot be accurately compared to each other as each subscale has a different number of items resulting in a different range of possible scores. Therefore, the comparisons are best based on derived scores: age-based scaled scores or composite scores[8].

Scaled scores represent a child's performance on a (sub)scale relative to the same age peers. They are derived from the total raw scores on each of the subscale and are scaled to a metric with a range of 1 to 19, a mean of 10 and a SD of 3.

Composite scores are scaled to a metric with a mean of 100 and a SD of 15, and range from 40–160.

For the Language and Motor Scale, composite scores are derived from the sums of age-corrected scaled scores. For each composite, the distribution of the sum of scaled scores is used to derive corresponding percentiles which are converted to composite scores with a mean of 100 and a standard deviation of 15.

For the Cognitive subdomain the scaled score to composite equivalent is a linear conversion from one scale (mean=10, SD=3) to another (mean=100, SD=15).

For the scaled scores and composite scores, the absolute values will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

The 3 composite scores (Cognitive, Language and Motor) will be displayed by cohort and treatment group in a bar chart.

14.4.2 Infant and Toddler Quality of Life Questionnaire (itqol-97, 2013) (ITQOL)

The Infant Toddler Quality of Life questionnaire (ITQOL) is an observer-reported outcome tool developed for use in children from 2 months to 5 years old that attempts to capture physical, mental and social well-being. The ITQOL adopts the World Health Organization's definition of health as a state of complete physical, mental and social well-being, and not merely the absence of disease. The ITQOL also assesses the quality of the parents/guardians' life. The 97-item full-length version (ITQOL) will be used for this study. ITQOL is waived for subjects < 2 months old.

Domains

The following domains are part of the ITQoL:

- Overall Health (1item)
- Physical abilities (10 items)
- Growth and development (10 items)
- Pain (3 items)
- Temperament and mood (18 items)
- Behavior (12 items)
- Global behavior (1 items)
- Getting on with others (15 items)
- Global health perceptions (11 items)
- Change in health (1 item)
- Parental impact emotional (7 items)
- Parental impact time (7 items)
- Family cohesion (1 item)

For the ITQOL, the exact number of items that can be missing differs depending on which section is being scored, though the general rule is that a section can be scored if at least half the responses in that section were completed.

Summary scores for the 13 domains (overall score) will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

The summary scores for Overall Health, Physical Abilities and Growth and Development will be displayed separately for the sentinel and randomized subjects by cohort and treatment group in a bar chart.

14.4.3 Function Independence Measure (WeeFIM) (Wee-FIM II Version 6.4)

The WeeFIM (Functional Independence Measure for children) instrument is a functional independence assessment tool that measures functional performance across three domains (self-care, mobility and cognition) from the caregiver's perspective.

Performance of a child on each of the individual items within the WeeFIM is assigned to one of seven levels on an ordinal scale that represent the function from complete and modified independence (levels 7 and 6) without a helping person to modified and complete dependence (levels 5 to 1) with a helping person.

If individual items (questions) within a domain are missing, the item result is imputed to 1, per guidance in The WeeFIM Clinical Guide v 6.49.

If all items for a domain score are missing the domain score is considered missing.

If a domain score is missing, the Total score is missing.

For each of the following domains and the total score, the absolute values at each scheduled visit, and change from baseline at each scheduled visit, will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively:

- Self-care Score (min score=8, max score=56)
- Mobility Score (min score=5, max score =35)
- Cognition Score (min score=5, max score=35)
- Total WeeFIM rating (min=18, max=126)

Domain and total scores will be listed by cohort, sentinel/randomized subjects, treatment group, and subject number.

Note: Although each domain will be summarized so that all aspects of this validated scale are reported, the cognition aspect of the WeeFIM (cognition subtotal score) is considered not to be of concern for subjects with achondroplasia.

The three domains and Total WeeFIM score will also be displayed by visit in a bar chart and presented separately for the sentinel and randomized subjects by cohort and treatment group.

14.5 Sleep Study Scores

A sleep study will be performed in a limited number of qualified sleep centers. A sleep-testing device will be used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea will include, but may not be limited to, the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index). Sleep study data is collected at Screening, Week 52, and early termination visit.

Following episodes of sleep apnea variables will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

- Number of episodes of apnea per hour (Apnea Index).
- Number of episodes of hypopnea per hour (Hypopnea Index).

- Number of episodes/Duration of obstructive apneas
- Number of episodes/Duration of central apneas
- Number of episodes/Duration of mixed apneas
- Number of episodes/Duration of obstructive hypopneas
- Number of desaturations

Listing of the above episode of sleep apnea variables will be provided.

15 SAFETY EVALUATIONS

The safety population will be used for all safety summaries.

Summary tables assessing safety parameters at planned visits over time will include all safety events up to 30 days following treatment discontinuation. These summary tables will be presented separately by cohort and overall by treatment group using format as specified in Table 5.4. Listings will include all reported data.

Safety will be assessed by examining the incidence, frequency, severity (determined using the CTCAE version 4.03), and relationship to study treatment of all TEAEs reported during the study period. In addition, changes from baseline in clinical laboratory results and vital signs will be assessed.

15.1 Adverse Events

Adverse events (AEs) will be coded in accordance with MedDRA Version 24.1 and performed prior to DBL. Coding of the severity of AEs is performed by the investigators using national cancer institute (NCI) CTCAE version 4.03, where events are coded from CTCAE Grade 1 to Grade 5.

Only TEAEs defined as any adverse event that newly appeared, increased in frequency, or worsened in severity following initiation of study treatment administration are reported by the investigators and consequently are included in the summary tables.

In the event that the start date of an AE is incomplete or missing, conservative imputation rules are applied so that where there is uncertainty, the event is considered treatment emergent. Similarly, the AE end dates are imputed in a conservative manner to a maximum length.

15.1.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4. In summaries by SOC and/or PT, subjects with more than one AE of the same SOC or PT will be counted once within that SOC/PT. For those AEs that occurred more than once during the study, AEs by severity will be summarized by the maximum CTCAE grade and by all CTCAE grades. The tables are ordered by the descending frequency of SOC or PT of overall in the table.

The following summary tables will be provided:

- Overview of the incidence of TEAEs

- Overview of exposure-adjusted event rates of TEAEs
- Incidence and exposure-adjusted event rates of TEAEs by SOC, PT, and CTCAE grade
- Incidence of TEAEs by SOC, PT and highest CTCAE grade
- Incidence of and exposure-adjusted event rates TEAEs by PT
- Incidence of TEAEs by SOC
- Incidence of and exposure-adjusted event rates treatment related TEAEs by SOC, PT and CTCAE grade
- Incidence of and exposure-adjusted event rates TEAEs with CTCAE Grade >= 3 by SOC, PT and CTCAE grade
- Incidence of serious adverse events (SAEs) by SOC and PT
- Incidence of non-serious adverse events by SOC and PT
- Incidence of TEAEs leading to study or study treatment discontinuation by PT
- Incidence of TEAEs leading to study treatment interruption by PT
- Incidence of TEAEs leading to study treatment dose reduction by PT
- Incidence of achondroplasia related TEAEs by SOC and PT*

* Achondroplasia-related TEAEs will be identified using the PTs identified for achondroplasia-related medical history (see Section 10). In addition, all AEs will be reviewed prior to DBL and the list updated as required.

For exposure-adjusted event rates of TEAEs, exposure will be derived to up to the last dose reported in the study database.

Listings:

In addition to the above tables, the following listings will be provided and ordered by subject and AE start date:

- All TEAEs
- TEAEs with CTCAE Grade ≥ 3
- Achondroplasia-related TEAEs
- SAEs
- Deaths
- TEAEs leading to study or study treatment discontinuation

- TEAEs leading to study treatment interruption or dose reduction
- TEAEs of confirmed/suspected COVID-19
- TEAEs due to COVID-19 Vaccine

15.1.2 Events of Interest

Events of interest (EOI) will be summarized by PT separately by cohort and overall by treatment group using format as specified in Table 5.4. For those AEs that occurred more than once during the study, the maximum severity will be used to summarize the AEs by severity.

The following are identified as events of interest:

Injection site reactions (ISR)

- TEAEs with a MedDRA High Level Term (HLT) of "Injection site reaction".

Hypotension

- TEAEs with PT: Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure orthostatic decreased, Blood pressure systolic decreased, Blood pressure systolic inspiratory decreased, Diastolic hypotension, Hypotension, Orthostatic hypotension.

Heart rate change

- TEAEs with a PT: Atrial tachycardia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Sinus tachycardia, Supraventricular tachycardia, Tachycardia, Tachycardia paroxysmal, Ventricular tachycardia, Bradycardia.

Hypersensitivity SMQ

- TEAEs with a PT included in the MedDRA hypersensitivity SMQ

Algorithmic Anaphylaxis SMQ (with sponsor-defined time restrictions)

- TEAEs with a PT included in the MedDRA anaphylactic reaction SMQ, with an additional time restriction: a narrow scope PT within 48 hours of a dose, or two broad scope PTs from different classes where both PTs are within 48 hours of the same dose.

Fractures

- TEAEs with a PT containing the term "fracture" and also PTs of Bone fragmentation, Bone fissure, Scapulothoracic dissociation and Flail chest

Slipped Capital Femoral Epiphysis (SCFE)

- TEAEs with a PT: Epiphyseal disorder, Epiphyseal injury

Avascular necrosis and osteonecrosis

- TEAEs with a PT: Osteonecrosis, Osteonecrosis of jaw, Osteonecrosis of external auditory canal, Necrosis ischaemic

Events of interest will be summarized as follows:

- Incidence and exposure-adjusted event rates of ISR events by PT
- Incidence and exposure-adjusted event rates of hypotension by PT
- Incidence and exposure-adjusted event rates of heart rate change events by PT
- Incidence and exposure-adjusted event rates of hypersensitivity (SMQ)
- Profile of ISRs
- Profile of hypotension
- Profile of heart rate change events

Profile summaries include: highest CTCAE grade, number of events per subject, time from first dose to first event onset, duration of events (days), action taken with study treatment, outcome of events.

Listings:

In addition to the above tables the following EOI listings are also provided:

- TEAEs of injection site reaction
- TEAEs of hypotension
- TEAEs of documented symptomatic hypotension
- TEAEs of heart rate change events
- TEAEs of hypersensitivity (SMQ)
- TEAEs of algorithmic anaphylaxis (SMQ) with sponsor-defined time restrictions
- TEAEs of fractures
- TEAEs of SCFE
- TEAEs of avascular necrosis and osteonecrosis

15.1.3 Injection Site Reaction Symptoms

Injection site reactions (ISRs) associated with single symptoms are recorded on the AE page (as a single symptom). ISRs with multiple symptoms are recorded as an AE of "Injection Site Reaction" on the AE page and the associated individual symptoms are recorded on the ISR symptom page.

In order to describe all ISR symptoms recorded, summaries will be based on the data collected on the ISR Symptoms page and also those single symptoms recorded as an adverse event.

Incidence and exposure-adjusted event rates of ISR Symptoms will be summarized by PT and separately by cohort and overall by treatment group using format as specified in Table 5.4.

ISR Symptoms will be listed.

15.2 Clinical Laboratory Tests

Clinical laboratory tests (hematology, chemistry, and urinalysis) are performed at Screening, and pre-dose at Day 1, Day 8, Week 3, Week 6, Week 20, Week 39, Week 52 and early termination visit.

All summary tables will include laboratory assessments from baseline up to 30 days post treatment discontinuation. Results will be reported separately as hematology, chemistry, urinalysis, and "other laboratory tests".

Laboratory tests will be graded as low/normal/high based on laboratory normal ranges. In addition, for laboratory tests with CTC grading available, all non-missing numeric results will be used to determine CTC grade programmatically, based on CTCAE v4.03.

For the following parameters, the distinction is made between significantly low/high results:

- Glucose (Hypoglycemia/Hyperglycemia)
- Hemaglobin (Anemia/Hemaglobin increased)
- Lymphocytes (Lymphocyte count decreased/Lymphocyte count increased)
- Potassium (Hypokalemia/Hyperkalemia)
- Sodium (Hyponatremia/Hypernatremia)
- Calcium (Hypocalcemia/Hypercalcemia)

The absolute values for pre-dose laboratory results at each scheduled visit, change from baseline in pre-dose laboratory results, and percent change from baseline in pre-dose laboratory results at each scheduled visit will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

Shift tables from baseline to worst post-baseline value (including scheduled and unscheduled visits) based on the CTC grading (Normal – Grade 5) will be generated for each Lab parameter where CTCAE grading is available, excluding parameters where CTCAE Grade does not rely on quantitative results alone (e.g. potassium and uric acid). Percentages are based on the number of subjects with each Baseline CTCAE grade (Normal, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, Missing, Overall). Shift tables will be produced separately by cohort and overall by treatment group using format as specified in Table 5.4.

For laboratory tests where grades are not defined by CTCAE, or where CTCAE grading does not rely on quantitative results alone (e.g. potassium and uric acid), shift tables will be generated using the low/normal/high classification to compare to baseline to the worst post-baseline value.

Line plots of the mean results (+/- SD) for the pre-dose windowed absolute values including all scheduled visits will be provided for the following parameters by treatment group by cohort. Data from the sentinel subjects and randomized subjects received active treatment within each cohort will be pooled:

- Hematology: erythrocytes, hematocrit, hemoglobin, leukocytes, neutrophils, platelets, WBC and RBC count.
- Chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin, blood urea nitrogen, calcium chloride, creatinine, direct bilirubin, glucose, lactate dehydrogenase, phosphate, potassium, protein, sodium, thyrotropin, vitamin D.

Listings:

In addition to the above tables, the following listings will be provided and will contain CTC grade and laboratory reference ranges:

- Hematology results
- Chemistry results
- Urinalysis results
- Urine chemistry results
- Other laboratory test results

- Laboratory results with CTCAE Grade ≥ 3

Listings will include all reported data and will be ordered by cohort, sentinel/randomized subject, subject ID, and assessment date.

15.3 Vital Signs

Vital Signs (heart rate, systolic/diastolic blood pressure, respiratory rate, and body temperature) are assessed at Screening, Day 1, Day 2, Day 3, Day 8, Week 3, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, safety follow-up visit, and early termination visit.

All summary tables will include vital signs recorded from baseline up to 30 days post treatment discontinuation.

The vital signs that are collected pre-dose and post-dose. Vital sign assessment frequency is shown below.

Table 15.3.1: Vital Sign Post-dose Assessment Frequency

Vital Sign Assessment Frequency				
Screening	After at least 5 min of rest, subject's vital signs are taken, preferably in sitting or supine position. Vital sign measurements should be repeated and documented 3 times with at least 5 min intervals between assessments.			
	Assessment Frequency			
Dosing Visits	**0-1 hr post-dose**	**0-2 hr post-dose**	**2-4 hr post-dose**	**4-8 hr post-dose**
Days 1, 2		q 15 min (± 5 min)	q 30 min (± 5 min)	q 60 min (± 10 min)
Days 3, 8		q 15 min (± 5 min)	q 30 min (± 5 min)	
Subsequent dosing visits	q 15 min (± 5 min); final assessment prior to end of visit (if longer than 1 hr)			

The absolute values for pre-dose vital signs at each scheduled visit, and change from baseline in pre-dose vital signs at each scheduled visit will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

Line plots will be generated, which present the mean pre-dose and post-dose absolute values (+/-SD) for each visit by treatment group by cohort. Data from the sentinel subjects and randomized subjects received active treatment within each cohort will be pooled.

The percentage of subjects experiencing at least one instance of a decrease of 20% in diastolic blood pressure from pre-dose to same-day post dose will be summarized for overall (each subject meeting criteria at any time in the study will be counted only once) for both sentinel subjects and randomized subjects.

Shift tables (Diastolic BP <40mmHg, Diastolic BP ≥40mmHg) from pre-dose to lowest same-day post-dose value category (Diastolic BP <40mmHg, Diastolic BP ≥40mmHg) will

be generated for overall (each subject meeting criteria at any time in the study will be counted only once) for both sentinel subjects and randomized subjects.

Shift tables (Diastolic BP <30mmHg, Diastolic BP ≥30mmHg) from pre-dose to same-day lowest post-dose value category (Diastolic BP <30mmHg, Diastolic BP ≥30mmHg) will be generated overall (each subject meeting criteria at any time in the study will be counted only once) for both sentinel subjects and randomized subjects.

Shift tables (Systolic BP < (70mmHg plus 2 x Age), Systolic BP ≥ (70mmHg plus 2 x Age)) from pre-dose to lowest same-day post-dose value category ((Systolic BP < (70mmHg plus 2 x Age), Systolic BP ≥ (70mmHg plus 2 x Age)) will be generated for overall (each subject meeting criteria at any time in the study will be counted only once). Subject's age used in this calculation is the integer value.

A listing of vital sign data will also be provided.

15.4 Biological Parental Standing Height

If available standing height of the subject's biological parents will be listed.

15.5 Electrocardiogram

Electrocardiogram (ECG) data are recorded at Screening, Day 1, Day 8, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, safety follow-up visit, and early termination visit.

ECG assessments are performed in triplicate on Day 1 (pre-dose and post-dose) and on study day visits (post-dose only).

Summaries will be provided over all planned assessments, and repeated with the requirement that all post-dose ECG assessments should occur around the expected time of CMax, i.e., 20-40 minutes post-dose. The mean results of the ECG assessments meeting these criteria will be used for summaries and analyses.

All measures and means of the measures will be included in the listings.

The following ECG results will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4 at scheduled visits:

- ECG Mean Heart Rate (beats/min)
- QT interval (msec)
- QTcF interval (msec)
- PR interval (msec)

- RR interval (msec)
- QRS Duration (msec)

The following endpoints will be summarized at scheduled visits, and across all time points (using the highest mean QTc value), and presented by cohort and overall by treatment group using format as specified in Table 5.4.

- Percentage of subjects with QTcF >450 to ≤480ms, >480 to ≤500ms, >500 msec

The following endpoints will be summarized at scheduled visits, and across all time points, and presented by cohort and overall by treatment group using format as specified in Table 5.4

- Percentage of subjects experiencing at least one instance of a (decrease in mean heart rate from pre-dose baseline >25% and a mean heart rate <50 beats/min) post-dose.
- Percentage of subjects experiencing at least one instance of an (increase in mean heart rate from pre-dose baseline >25% and a mean heart rate >100 beats/min) post-dose.

The following endpoints will be summarized across all time points and presented by cohort and overall by treatment group using format as specified in Table 5.4.

- Percentage of subjects with a QTcF increase of 60ms from pre-dose baseline at any time
- Percentage of subjects with QTcF changes from pre-dose baseline of >30 and ≤ 60 msec, or >60 msec at any time

Listings will be provided and ordered by cohort, sentinel/randomized subject, treatment group, and visit:

- All ECG results.
- All ECG results for subjects with a QTc increase of 60msec from pre-dose baseline.

15.6 HPA Axis Assessments

To address potential effects of vosoritide on activation of the hypothalamic pituitary (HP) axis, assessment of salivary cortisol and serum prolactin levels will be analyzed at baseline, Week 26, Week 52 and early termination visit.

This data will be listed.

15.7 Child Behavior Checklist (Achenbach, 2000)

The Child Behavior Checklist (CBCL) 1.5- 5 years questionnaire is captured at Screening, Week 26, Week 52, and early termination visit.

All summaries will be generated on the Safety Population and include all assessments recorded up to 30 days following treatment discontinuation. Listings will include all reported data.

The CBCL 1.5-5 years old comprise questions addressing symptoms related to mood, behavior issues, and sleep disturbance. It is completed by the parent or primary caregiver.

The CBCL 1.5-5 years old consists of 100 questions, scored on a three-point Likert scale (0=Not True (as far as you know), 1= Somewhat or Sometimes True, 2=Very True or Often True). The time frame for item responses is the past 2 months.

Note: No data is collected from the language scale, as it is supplemental and not required to calculate any of the behavior measures.

The checklist yields scores in the following areas: emotionally reactive, anxious/depressed, withdrawn, somatic complaints, sleep problem, attention problems, and aggressive behavior.

The table in Appendix 25.2 shows how the domains are constructed with regards to the individual questions. The scores for each individual question within a domain are summed to give a domain score.

Each domain score above and total score will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4 at Baseline, Week 26 and Week 52 as well as change from baseline at Week 26 and Week 52 (where baseline measures exist).

Domain scores and total score will be listed by cohort, sentinel/randomized subjects, treatment group, and subject ID.

15.8 Echocardiogram

Echocardiogram results are only collected at the Screening visit, at safety follow up, and early termination visit if the previous assessment was done more than 3 months prior to early termination and will be listed by cohort, sentinel/randomized subjects, treatment group, and subject ID.

15.9 On-Study Procedures, Interventions and Surgeries

Any procedures, interventions of surgeries that occur on study (post first dose of study treatment) will be captured, along with start and stop date. These will be coded using MedDRA version 24.1 and will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4, and details provided in a listing.

15.10 Hip Monitoring and Rotation

All hip monitoring clinical assessments, including hip rotation, will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID, and assessment date.

15.11 Body Mass Index and BMI Z-scores

Weight (kg) and standing height are collected at Screening, Day 1, Day 2, Day 3, Day 8, Week 3, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, and early termination visit.

Standing height are recorded at Screening, Day 1, Week 6, Week 13, Week 26, Week 39, and Week 52.

Body Mass Index (BMI) will be calculated at each visit as:

$$\text{Body Mass Index (kg/m}^2) = \frac{Weight\ (kg)}{Height\ (m)2}$$

In calculation of BMI, in case standing height is not measured and body length is available, a derived standing height will be calculated; refer to Section 15.11.

Only for subjects aged 24 months or older, each measurement of BMI will be converted to an age-and sex-appropriate standard deviation score (SDS), also referred to as a Z-score, by comparison with reference data available for average stature children from the Centers for Disease Control and Prevention (CDC). The derived height mentioned above for BMI is also used for BMI in the calculation of BMI Z-score.

The absolute values at baseline, each 6-month visit, and change from baseline at each 6-month visits will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4 for both BMI and BMI Z-Score (again though, BMI Z-score will only be calculated for subjects aged 24 months or older).

All assessments will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID and visit.

15.12 Weight Z-Scores

Weight (kg) is measured at Screening, Day 1, Day 2, Day 3, Day 8, Week 3, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, and early termination visit.

Each measurement of weight will be converted to an age-and sex-appropriate SDS, also referred to as Z-score, by comparison with reference data available for average stature children from the CDC.

The weight of the subject on Day 1 will be used as the baseline measure, regardless of whether this is recorded pre or post-dose.

The absolute values and change from baseline at scheduled visits will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

All assessments will be listed for by cohort, sentinel/randomized subjects, treatment group, subject ID, and visit.

16 IMAGING SECONDARY ENDPOINT(S)

Imaging will be performed at screening, Week 52, and early termination visit:

Dual energy X-ray absorptiometry of whole body and spine

Anterior-posterior and lateral lumbar spine X-rays

Anterior-posterior X-rays of lower extremities

MRI data will be performed at screening, Week 52, and early termination visit to evaluate the effect of vosoritide on skull and brain morphology, including face, foramen magnum, ventricular, and brain parenchymal dimensions.

All summaries of imaging data and MRI data will be generated on the FAS and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

16.1 Lower Limb X-Rays

For each of the following parameters, the absolute values for both the left and right leg at Baseline and Week 52, and change from baseline at Week 52 will be summarized by cohort and overall by treatment group using the format as specified in Table 5.4:

- Left/Right Femur length (cm)
- Left/Right Fibula length (cm)
- Left/Right Tibia length (cm)
- Left/Right Tibia bowing angle (degrees)
- Left/Right Distance between ankle joint and distal growth plate of fibula (cm)
- Left/Right Lower Extremity (cm)
- Ratio of Left/Right Femur length (cm) to Tibia length (cm)
- Ratio of Left/Right Tibial length (cm) to Fibula length (cm)

In addition, change from baseline in tibial length (y-axis) at Week 52 will be presented on boxplots with a separate box for each leg and treatment group on the x-axis by cohort. Similar plots will also be generated for change from baseline in fibula length.

All assessments will be listed by cohort, treatment group, subject and visit.

16.2 Lumbar Spine X-Rays

Lumbar spine x-rays (AP and lateral views) assessments will be listed by cohort, treatment group, subject and visit.

16.2.1 Vertebral Height

Vertebral heights (anterior, medial, and posterior) will be measured for each individual vertebra (L1, L2, L3, L4, and L5).

The following ratios will be calculated for each individual vertebra (L1, L2, L3, L4, and L5) and reported to 1 decimal place:

- Anterior height (cm) to medial height (cm)
- Anterior height (cm) to posterior height (cm)
- Medial height (cm) to posterior height (cm)

For each of the vertebral height and the above ratios, the absolute values at Baseline and Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

16.2.2 Transverse Diameter (Interpedicle Distance)

The transverse diameter (interpedicle distance) will be measured for each individual vertebra (L1, L2, L3, L4, and L5).

For each transverse diameter vertebra, the absolute values at Baseline, Week 52, and the change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

In addition, change from baseline in transverse diameter (y-axis) for each individual vertebra (x-axis) will be presented on a boxplot at Week 52 for each cohort and treatment group.

16.2.3 Sagittal Width

The spinal canal width (sagittal width) will be measured for each individual vertebra (L1, L2, L3, L4, and L5).

For each individual vertebra, the absolute values at Baseline, Week 52, and the change from baseline Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

In addition, change from baseline in sagittal width (y-axis) for each individual vertebra (x-axis) will be presented on a boxplot at Week 52 for each cohort and treatment group.

16.2.4 Lumbar Spine Angles

The following angles will be measures on the lumbar spine x-rays:

- Sacral tilt (degrees)

- Lordosis (inward curve of the spine) (degrees)
- Kyphosis (convex curvature of the spine) (degrees)

Each angle will be measured on the spine x-rays and compared to Baseline at Week 52 to determine any worsening of sacral tilt, lordosis (inward curve of the spine) or kyphosis (convex curvature of the spine).

The absolute values of the sacral tilt, lordosis and kyphosis angles at Baseline, Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

A worsening in sacral tilt angle compared to baseline will be summarized [n(%)] by cohort by treatment group and overall at Week 52 as follows:

- Percentage of subjects with an increase in sacral tilt angle of ≥5 to < 10 degrees
- Percentage of subjects with an increase in sacral tilt angle of ≥ 10 degrees

A worsening in lumbar lordosis compared to baseline will be summarized [n(%)] by cohort by treatment group and overall at Week 52 as follows:

- Percentage of subjects with an increase in lordosis angle of ≥5 to < 10 degrees
- Percentage of subjects with an increase in lordosis angle of ≥ 10 degrees

A worsening in kyphosis angle compared to baseline will be summarized [n(%)] by cohort by treatment group and overall at Week 52 as follows:

- Percentage of subjects with an increase in kyphosis angle of ≥5 to < 10 degrees
- Percentage of subjects with an increase in kyphosis angle of ≥ 10 degrees

A listing of subjects experiencing a worsening in sacral tilt, kyphosis or lordosis will be provided.

16.3 Dual Energy X-ray Absorptiometry

A dual energy x-ray absorptiometry (DXA) scan is performed at Baseline and Week 52, in order to collect relevant BMC/BMD data (including Z-scores) for whole body less head, and the lumbar spine.

All DXA data will be summarized separately by cohort and overall by treatment group using the format as specified Table 5.4 for each scanner manufacturer (GE - Lunar Prodigy or Hologic – Discovery Horizon). Changes over time can only be interpreted if subjects use the same scanner consistently throughout the study. Subjects will be summarized according to the scanner used for their Baseline assessment. Subjects who have results from more than

one scanner type will be excluded from summaries, and their data will be listed only. All data will be listed.

16.3.1 Whole Body Less Head and Lumbar Spine

The absolute values at Baseline and Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4 for the following measures of bone mineral content (BMC) and bone mineral density (BMD):

- Whole Body Less Head BMC (g)
- Whole Body Less Head BMD (g/cm^2)
- Whole Body BMC (g)
- Whole Body BMD (g/cm^2)
- Lumbar Spine BMC (g)
- Lumbar Spine BMD (g/cm^2)

BMD Z-scores will be provided in the DXA reports, and the absolute values at Baseline and Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4 by scanner for each of the following:

- Whole Body Less Head BMD Z-Score
- Whole Body BMD Z-Score
- Lumbar Spine BMD Z-Score

The absolute values of total body percent fat, android percent fat, and gyenoid percent fat will be listed.

Box plots of whole body less head BMD Z-scores will be provided by cohort by treatment group and scanner.

16.4 MRI

For each of the following parameters and ratios, the absolute values and change from baseline at Week 52 will be summarized by cohort and overall by treatment group using the format as specified in Table 5.4:

Volume of Face

Volume of Sinus

Volume of Calvarium

Area of Foramen Magnum

Area of Spinal Cord at the FM Level

Whole Brain Total Volume

Ventricles Total Volume

Ratio of Face volume to Calvarium

Ratio of Area of Spinal Cord to Foramen Magnum

Ratio of Face volume to Sinus

MRI assessments for above variables, evidence of cervicomedullary, and spinal cord compression will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID and visit.

17 BONE METABOLISM BIOMARKERS

Bone metabolism biomarkers (both blood and urine) will be collected to assess changes in bone metabolism. The safety population will be used for all summaries.

Serum samples for bone metabolism blood biomarkers (collagen X and bone-specific alkaline phosphatase [BSAP]) are collected pre-dose at baseline, Day 8, Week 6, Week 20, Week 39, early termination visit. Urine samples for bone metabolism urine biomarkers (Cross-linked C-Telopeptide of Collagen Type II [CTX-II]) are collected pre-dose on Day 1, Day 2, Day 3, Week 3, Week 13, Week 26, Week 39, Week 52, and early termination visit.

For BSAP and Collagen X, the absolute values, and change from baseline at scheduled visits will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4.

For CTX-II, the absolute values normalized by creatinine, and change from baseline at scheduled visits will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4.

A box plot of change from baseline in BSAP, Collagen X, CTX-II normalized by urine creatinine over time will be provided for pooled sentinel subjects and randomized subjects received active treatment.

Bone metabolism biomarkers will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID, and visit.

18 VOSORITIDE PD ACTIVITY BIOMARKERS

Samples for vosoritide activity urine biomarkers (cyclic guanosine monophosphate [cGMP] and urine chemistry (urine creatinine test) are collected pre-dose and post-dose (approximately 2-4 hours after study treatment administration) when possible, on Day 1, Day 2, Day 3, Week 3, Week 26, Week 39, Week 52, and early termination visit. Each urine collection will be tested for biomarker concentration and urine creatinine concentration for normalization.

The absolute values for pre-dose and post-dose urine cGMP normalized by creatinine at each scheduled visit and change from pre-dose to post-dose time points at each scheduled visit will be summarized and presented by cohort and overall by treatment group using format as specified in Table 5.4.

When possible, plasma PK samples with sufficient residual volume after completion of PK analysis will be used to measure changes in plasma cGMP after dose administration. Plasma samples will be collected for PK analysis on Day 1, Week 13, Week 26, Week 39, and Week 52. Plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose on scheduled visits. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes.

The absolute values for pre-dose and post-dose plasma cGMP at each scheduled visit and change from pre-dose to post-dose time points at each scheduled visit will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

A box plot for the maximum change from pre-dose of plasma cGMP and change from pre-dose of urine cGMP normalized by creatinine by cohort by treatment group by visit will be provided.

Vosoritide activity urine biomarkers will be listed by cohort, sentinel/randomized subjects, treatment group and subject ID.

19 IMMUNOGENICITY ASSESSMENT

Serum samples for anti-drug antibody (ADA) testing will be drawn pre-dose on Day 1, Week 3, Week 13, Week 26, Week 52, and early termination visit. Blood (serum) samples for testing drug-specific IgE will be drawn on Day 1 and in the event of a Grade 3 or significant hypersensitivity adverse event, or at the investigator's discretion.

ADA testing will include anti-vosoritide total antibody (TAb); TAb cross-reactive with endogenous C-type natriuretic peptide (CNP), brain natriuretic peptide (BNP) or atrial natriuretic peptide (ANP); and anti-vosoritide neutralizing antibody (NAb).

NAb testing and TAb testing for cross-reactivity with endogenous CNP, ANP or BNP will be performed only on baseline and TAb positive samples. NAb testing will not be performed if the corresponding TAb is negative. A listing for each ADA assay will be provided.

Summary tables will include all safety events up to 30 days following treatment discontinuation. Listings will include all reported data.

The immunogenicity population will be used for all summaries. The data conversion rules for immunogenicity analysis are listed below:

Operational Data Conversion Table for Immunogenicity Analysis

Assay	Result Type	Result = "Concentration (Titer Units)"	Pos/Neg for Incidence Table	Numerical Value for Display	Numerical Value for Calculation
Anti-BMN111 TAb	Numeric Titer	Negative Screen	Negative	1	0
		Negative Immunodepletion	Negative	1	0
		Negative Titer (≤10)	**Negative**	**1**	**0**
		* Value * (e.g. 20, 30, …)	**Positive**	**e.g. 20, 30, …**	**e.g. 20, 30, …**
		Imputed values - none			
		MRD of assay: 10			
Anti-BMN111 NAb	Numeric Titer	Negative Screen	Negative	1	0
		Negative Immunodepletion	Negative	1	0
		Negative Titer (≤5)	**Negative**	**1**	**0**
		* Value * (e.g. 10, 20, …)	**Positive**	**e.g. 10, 20, …**	**e.g. 10, 20, …**
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			
		MRD of Assay: 5			
ANP Reactivity	Binary	Negative Screen	Negative		
		Negative Immunodepletion	Negative		
		Positive Immunodepletion	**Positive**		
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			
BNP Reactivity	Binary	Negative Screen	Negative		
		Negative Immunodepletion	Negative		
		Positive Immunodepletion	**Positive**		
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			
CNP-22 Reactivity	Binary	Negative Screen	Negative		
		Negative Immunodepletion	Negative		
		Positive Immunodepletion	**Positive**		
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			

The incidence [n(%)] of TAb titer positive results will be summarized for each scheduled visit, and overall (described as 'Ever Positive') as follows:

$$\frac{Number\ of\ subjects\ with\ a\ positive\ test\ result}{Number\ of\ subjects\ with\ non-missing\ TAb\ result} * 100$$

The incidence [n(%)] of NAb positive test results, and positive cross-reactivity results for ANP, BNP and CNP, will also be calculated based on the number of subjects with a non-missing TAb result, and summarized at each scheduled visit and overall.

The absolute values (numerical values) of TAb titers and NAb titers will be summarized at Day 1, Week 3, Week 13, Week 26, and Week 52, and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

The mean (SD) TAb titer, number of hypersensitivity adverse events (HAEs) excluding injection site reactions, and number of subjects experiencing HAE's will be summarized by the highest HAE CTCAE Grade, and presented by TAb status (negative or positive) and separately by cohort and overall by treatment group using format as specified in Table 5.4.

A line graph of the mean TAb titer (+/- SE) will be presented over time for each visit by pooled placebo, active for each cohort (pooled for sentinel and randomized subjects), and overall. A similar figure will be generated for NAb titers.

The relationship between immunogenicity (ADA status: negative or positive) and measures of safety and efficacy will further be presented graphically by treatment group:

- Box plot of change from baseline at week 52 in standing height/body length Z-Score by TAb status
- Box plot of change from baseline at week 52 in standing height/body length Z-Score by NAb status
- Box plot of change from baseline at week 52 in standing height/body length by by TAb status
- Box plot of change from baseline at week 52 in standing height/body length by NAb status
- Box plot of number of hypersensitivity adverse events by TAb status
- Box plot of number of hypersensitivity adverse events (excluding ISRs) by TAb status
- Box plot of number of injection site reaction adverse events by TAb status

- Box plot of maximum duration of injection site reaction adverse event by TAb status, where injection site hemorrhage, injection site hematoma, injection site bruising, and injection site induration will be excluded.

Should there be a significant relationship between TAb positivity and change from baseline at Week 52 in standing height/body length, a scatter plot of change from baseline in standing height/body length at Week 52 versus mean TAb titer in TAb positive subjects will be presented as a second tier analysis. The Pearson correlation coefficient will be included in the figure to describe the association.

In addition, the following listings will be provided:

- Total antibody titers and neutralizing antibody titers
- Hypersensitivity adverse events with antibody results
- Drug-specific IgE, total IgE, C4 and serum tryptase for hypersensitivity reaction visits
- Mean Tab and NAb titers, standing height/body length, standing height/body length Z-Scores, and AGV
- TAb cross reactivity to endogenous natriuretic peptides
- TAb cross reactivity by subject and cardiac disorder or HLGT ‘fluid and electrolyte imbalance’ related adverse event.

All immunogenicity listings will be ordered by cohort, sentinel/randomized subjects, treatment group, 4-digit subject ID (i.e., the subject ID excluding the site number), and visit.

20 PHARMACOKINETICS AND PHARMCODYNAMICS

Vosoritide concentrations and PK parameters will be summarized descriptively by visit for all subjects in the PK population. If supported by the data, impact of demographics and immunogenicity on PK parameters and the exposure-response relationship between vosoritide exposure and efficacy, biomarker, and safety pharmacodynamic (PD) endpoints of interest will be explored. Details on the PK and PK/PD analyses are separately documented in the Clinical Pharmacology Analysis Plan.

21 OTHER ANALYSES

To evaluate the impact of COVID-19 pandemic on the study conduct and results (assumed started from 1st January 2020 up until the date of data finalization), the following new outputs will be presented separately by cohort and overall by treatment group using format as specified in Table 5.4:

1. For all protocol scheduled visits, number of missed visits, late visits, and clinical site visits changed to virtual or home visits due to COVID-19 will be summarized.
2. COVID-19 has been added to the new MedDRA version 24.1. One AE listing will be produced that will include all AEs coded to Preferred Terms containing “COVID-19”. Another AE listing will be produced that will be included all AEs due to COVID vaccine.
3. A listing of concomitant medication of COVID vaccine will be provided.
4. COVID-19 specific protocol deviations will be listed and summarized.

22 ANALYSES DIFFERENT FROM PROTOCOL-DEFINED ANALYSES

Standing height/body length was one of the growth measurements included in the secondary efficacy endpoints in the protocol. It is the first key secondary efficacy endpoint in this SAP.

23 REFERENCES

Achenbach, T. M., & Rescorla, L. A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley–III) Technical Manual

Health Act CHQ: Infant and Toddler Quality of Life Questionnaire – 97 (itqol-97) © 2013

Hoover-Fong, JE, Schulze, KJ, McGready, J, Barnes, H et. al. Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height. Am J ClinNutr 88[2], 364-371. 2008.

https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

Uniform Data System for Medical Rehabilitation. 2016. *The WeeFIM II® Clinical Guide, Version 6.4*. Buffalo: UDSMR.

24 SUMMARY OF KEY CHANGES TO STUDY SAP

Version		Affected Section	Summary of Revisions
Number	Date		
1.1	17Nov2021	Section 14.1	Option OBSMARGINS was added in the PROC MIXED procedure.
1.1	17Nov2021	Section 15.1.2	Definition for Algorithmic Anaphylaxis SMQ has been updated.
1.1	17Nov2021	Section 19	"by cohort" was removed for box plots. Box plot for maximum severity of hypersensitivity adverse events by TAb status was removed. Injection site hemorrhage, injection site hematoma, injection site bruising, and injection site induration will be excluded for the box plot of maximum duration of injection site reaction adverse event by TAb status.

25 APPENDICES

25.1 Summary of Growth Measures Derivations

Derived Value:	Measure required in calculation:	Age	Order of Substitution for measure required: 1 then 2.	
			1	2
BMI	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
AGV	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
Standing Height	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
Sitting Height	Height	Under 24 months	Crown-to-Rump Length	Sitting Height
		24 months or older	Sitting Height	Crown-to-Rump Length
Height Z-score*	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
BMI Z-score**	BMI	Under 24 months	Will not be calculated	
		24 months or older	Standing Height	Body Length
Lower Body Length	Standing Height and Sitting Height	Under 24 months	Body Length - Crown-to-Rump Length	Standing Height - Sitting Height
		24 months or older	Standing Height - Sitting Height	Body Length - Crown-to-Rump Length
Arm Span to Height Ratio	Height	Under 24 months	Body Length	Standing Height

Derived Value:	Measure required in calculation:	Age	Order of Substitution for measure required: 1 then 2.	
			1	2
		24 months or older	Standing Height	Body Length
Upper to Lower Body Segment Ratio	Upper Body: Lower Body	Under 24 months	Crown-to-Rump Length: (Body Length - Crown-to-Rump Length)	Sitting Height: (Standing Height - Sitting Height)
		24 months or older	Sitting Height: (Standing Height - Sitting Height)	Crown-to-Rump Length: (Body Length - Crown-to-Rump Length)

*Height Z-scores will be derived using CDC references and macro.

**BMI Z-score will be calculated in the age appropriate CDC macros, only for subjects aged 24 months or older.

Programming will not supply the BMI value that we derive for our datasets and table summaries to this macro.

The CDC macro will calculate BMI Z-scores using the Height value supplied as describe above to create the Height Z-scores. Therefore, the BMI Z-scores will be consistent with the Height Z-score.

25.2 Child Behavior Checklist Domains

Domain/Subscale	CBCL 1.5-5
EMOTIONALLY REACTIVE	21. Disturbed by change 46. Twitches 51. Panics 79. Shifts between sad-excite 82. Sudden mood change 83. Sulks a lot 92. Upset by new 97. Whining 99. Worries
ANXIOUS/DEPRESSED	10. Too dependent 33. Feelings easily hurt 37. Upset when separated 43. Looks unhappy 47. Nervous 68. Self-conscious 87. Fearful 90. Unhappy, sad, depressed
WITHDRAWN	2. Acts too young 4. Avoids eye contact 23. Doesn't answer 62. Refuses active games 67. Unresponsive to affection 70. Little affection 71. Little interest 98. Withdrawn
SOMATIC COMPLAINTS	1. Aches, pains 7. Can't stand things out of place 12. Constipated 19. Diarrhea 24. Doesn't eat well 39. Headaches 45. Nausea 52. Painful bowel movements 78. Stomachaches 86. Too concerned with neatness 93. Vomits
SLEEP PROBLEMs	22. Doesn't want to sleep alone 38. Trouble sleeping 48. Nightmares 64. Resists bed 74. Sleeps little 84. Talks, cries in sleep 94. Wakes often

Domain/Subscale	CBCL 1.5-5
ATTENTION PROBLEMS	5. Can't concentrate 6. Can't sit still 56. Clumsy 59. Quickly shifts 95. Wanders away
AGGRESSIVE BEHAVIOR	8. Can't stand waiting 15. Defiant 16. Demands must be met 18. Destroys others things 20. Disobedient 27. Lacks guilt 29. Easily frustrated 35. Gets in fights 40. Hits others 42. Hurts unintentionally 44. Angry moods 53. Attacks people 58. Punishment doesn't change behavior 66. Screams 69. Selfish 81. Stubborn 85. Temper 88. Uncooperative 96. Wants attention

105 Digital Drive

Novato, CA 94949

Statistical Analysis Plan

Study 111-206

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Vosoritide in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months

Version 2: Final CSR

Date: 02February2022

1 SAP SYNOPSIS

TITLES OF STUDY: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of vosoritide in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months.
PROTOCOL NUMBER: 111-206
STUDY SITES: Approximately 10-15 clinical centers worldwide
PHASE OF DEVELOPMENT: Phase 2
OBJECTIVES: The primary objectives of the study are to: • Evaluate the safety and tolerability of vosoritide in children age 0 to < 60 months with Achondroplasia (ACH) • Evaluate the effect of vosoritide on change from baseline in standing height/body length Z-Score The secondary objectives of the study are to: • Evaluate the effect of vosoritide on change from baseline in standing height/body length, annualized growth velocity (AGV), and upper: lower segment body ratio throughout the 52-weeks of the study • Evaluate the effect of vosoritide on other growth parameters and body proportions • Evaluate the effect of vosoritide on bone morphology/quality by X-ray and dual X-ray absorptiometry (DXA) • Evaluate the Pharmacokinetics (PK) of vosoritide in children age 0 to < 60 months with ACH • Evaluate hip function • Evaluate for hip, thigh, or knee pain, or change in gait • Evaluate the effect of vosoritide on health-related quality of life (HRQoL), developmental status, and functional independence using age-specific QoL and functional independence questionnaires (Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III], Activity of Daily Living and Functional Independence Measure (Wee-FIM), Infant Toddler Quality of Life Questionnaire (ITQOL), Child Behavior Checklist (CBCL) • Evaluate immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures • Evaluate the effect of vosoritide on bone metabolism and vosoritide pharmacodynamic (PD) biomarkers • Evaluate the effect of vosoritide on sleep apnea • Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions

- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

The exploratory objectives of the study are to:

- Document physical and phenotypic changes with clinical photography (optional)
- Evaluate genomic biomarkers (optional).

The exploratory objectives of the study are optional and will not be addressed in this SAP.

STUDY DESIGN AND PLAN: Study 111-206 is a phase 2 randomized, double-blind, placebo-controlled clinical trial of vosoritide in infants and younger children with a diagnosis of ACH.

Approximately 70 Subjects will be enrolled into 3 age cohorts: n ≥ 30 total for aged ≥ 24 to < 60 months, n ≥ 20 total for aged ≥ 6 to < 24 months, and n ≥ 20 total for aged 0 to < 6 months. There will be 3 sentinel subjects for each cohort, and the rest of subjects will be randomized 1:1 to treatment or placebo control and stratified by age for Cohorts 1 and 2.

All subjects who complete the 111-206 study will be eligible to receive vosoritide in the extension study 111-208 after the Week 52 visit.

ANALYSIS POPULATIONS:

The Full Analysis Set (FAS) is defined according to the intent-to-treat principle and includes all enrolled sentinel and randomized subjects with a signed informed consent.

The Per-Protocol (PP) population is defined as a subset of the FAS population who completed the treatment originally allocated (i.e., always received the assigned treatment), with a standing height/body length assessment at Week 52 following the protocol window, and with treatment compliance of at least 80%.

The Safety Population is a subset of the FAS who receive at least one dose of vosoritide or placebo in this study.

The PK Population is defined as all sentinel subjects and subjects randomized to vosoritide treatment group, who received at least one dose of vosoritide in this study and have at least one evaluable PK concentration.

The Immunogenicity Population is defined as all subjects in the Safety Population who have at least one evaluable immunogenicity sample.

STUDY ENDPOINTS AND ANALYSES:

Efficacy endpoints and analyses:

The primary efficacy endpoint is change from baseline in standing height/body-length Z-Score at Week 52.

The key secondary efficacy endpoints include change from baseline at Week 52 in standing height/body length, AGV, and upper to lower body ratio. Other secondary efficacy endpoints include biomarker samples to evaluate the effect of vosoritide on bone metabolism, vosoritide pharmacodynamic biomarkers, growth parameters and body proportions, sleep apnea, skull and brain morphology, and clinical outcome assessments (developmental/functional/HRQoL status).

In addition to the summary statistics analyses for efficacy endpoints, model-based analysis will be conducted for change from baseline at Week 52 in standing height/body length Z-Score, standing height/body length, AGV, and upper to lower body ratio for all cohorts overall and/or by cohort, as appropriate.

Safety endpoints and analyses:

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 and presented by System Organ Class (SOC) and Preferred Term (PT). Summaries of AE's will include all AE's, serious adverse events (SAEs) and events of interest (EOI).

Clinical laboratory tests will be summarized descriptively. Shift tables tabulating Common Terminology Criteria for Adverse Events (CTCAE) severity grade at baseline versus worst post-baseline grade will be provided.

Vital signs will be summarized descriptively. Shift tables tabulating shifts from pre-dose (diastolic blood pressure (BP) < 40 mmHg, diastolic BP ≥ 40mmHg) to lowest post-injection value (diastolic BP ≥40mmHg) will be provided. Additional shift tables will describe similar pre/post injection shifts in vital signs.

X-rays and DXA will be performed on the extremities and spine to evaluate changes in bone morphology and quality.

Anti-vosoritide immunogenicity assessments will be summarized descriptively. Behavioral assessments with the CBCL will be summarized descriptively.

Other analyses:

Additional analyses will be conducted as appropriate to evaluate the impact of the COVID-19 pandemic on the study conduct.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2 APPROVAL (SIGNATURE AND DATE)

(Signatures and dates are in the last page of this SAP)

Statistical Science	DD MON YYYY
Data Analytical Science	DD MON YYYY
Clinical Science Lead	DD MON YYYY
Pharmacovigilance Lead	DD MON YYYY
Head of Statistical Science	DD MON YYYY
Head of Clinical Science	DD MON YYYY

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
µg/kg	microgram/kilogram
ACH	achondroplasia
ADA	anti-drug antibody
AE	adverse event
AGV	annualized growth velocity
ANCOVA	Analysis of covariance
ANP	atrial natriuretic peptide
ATC	Anatomical Therapeutic Chemical
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BMN	BioMarin
BNP	brain natriuretic peptide
BP	blood pressure
BSAP	bone-specific alkaline phosphatase
CBCL	Child Behavior Checklist
CDC	Centers for Disease Control and Prevention
CM	concomitant medication
CRF	case report form
cGMP	cyclic guanosine monophosphate
CNP	C-type natriuretic peptide
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (v4.03)
CTX-II	C-terminal telopeptide of cross-linked collagen type II
DBL	database lock
DMC	data monitoring committee
DXA	dual x-ray absorptiometry
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
JNDA	Japan New Drug Application

HPA	hypothalamic pituitary adrenal
HRQoL	health-related quality of life
ISR	injection site reaction
ITQoL	Infant Toddler Quality of Life Questionnaire
IXRS	interactive web or voice response system
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCI	National Cancer Institute
NDA	New Drug Application
PD	pharmacodynamic
PK	pharmacokinetic
PP	per protocol
PT	preferred term
QTc-F	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SCFE	slipped capital femoral epiphysis
SD	standard deviation
SDS	standard deviation score
SE	standard error
SMQ	Standardized MedDRA query
SOC	system organ class
Tab	total anti-drug antibody
TEAE	treatment-emergent adverse event
TLGs	tables, listings, and graphs
WeeFIM	Activity of Daily Living and Functional Independence Measure
WHO	World Health Organization

4 INTRODUCTION

Study 111-206 (original protocol effective date: 06 December 2017) is a Phase 2 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of vosoritide in infants and young children with ACH, aged 0 to < 60 months.

This SAP is based on Amendment 2 of Study 111-206 (date: 08 February 2019). It describes the analyses and evaluations that will be provided for the final clinical study report (CSR). The final Version 2.0 of the SAP incorporates feedback from the Food and Drug Administration (FDA) received on Version 1.1 of the SAP (date: 17 November 2021), which was received on 19 January 2022. Any additional changes are provided in the table in Section 24.

Where there are major differences between the protocol-defined analyses, and the SAP-defined analyses, these will be identified in the SAP. The SAP-defined analyses prevail.

4.1 Objectives of Study

The primary objectives of study are to:

- Evaluate the safety and tolerability of vosoritide in children age 0 to < 60 months with ACH
- Evaluate the effect of vosoritide on change from baseline in standing height/body length Z-Score (height Z-Score may be used interchangeable)

The secondary objectives of study are to:

- Evaluate the effect of vosoritide on change from baseline in standing height/body length, AGV, and upper: lower body segment ratio throughout the 52 weeks of the study
- Evaluate the effect of vosoritide on other growth parameters and body proportions
- Evaluate the effect of vosoritide on bone morphology/quality by x-ray and DXA
- Evaluate the PK of vosoritide in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of vosoritide on HRQoL, developmental status, and/functional independence using age-specific QoL and functional independence questionnaires/QOL status (Bayley-III), Wee-FIM, ITQOL, and CBCL
- Evaluate immunogenicity of vosoritide and assess impact on safety, PK, and efficacy measures

- Evaluate the effect of vosoritide on bone metabolism and vosoritide PD biomarkers
- Evaluate the effect of vosoritide on sleep apnea
- Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

The exploratory objectives are to:

- Documental physical and phenotypic changes with clinical photography (optional)
- Evaluate genomic biomarkers (optional)

The exploratory objectives of the study are optional and will not be addressed in this SAP.

4.2 Study Design

Study 111-206 is a phase 2 stratified randomized, double-blind, placebo-controlled clinical trial of vosoritide in infants and younger children with a diagnosis of ACH.

Subjects aged ≥ 6 months to < 60 months old who have documented ACH confirmed by genetic testing; at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry; and who meet the study eligibility criteria, will participate. Eligible subjects ranging from 0 months to < 3 months old may enroll directly into 111-206 and have a minimum of 3 months of pre-treatment observation prior to commencing treatment with investigational product or may enroll in 111-901 for a minimum of 3 months of pretreatment growth assessment immediately before roll-over to 111-206.

Approximately 70 subjects will be enrolled at approximately 10-15 clinical centers worldwide.

Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive vosoritide, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 months to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive vosoritide, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)

- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who receive vosoritide, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

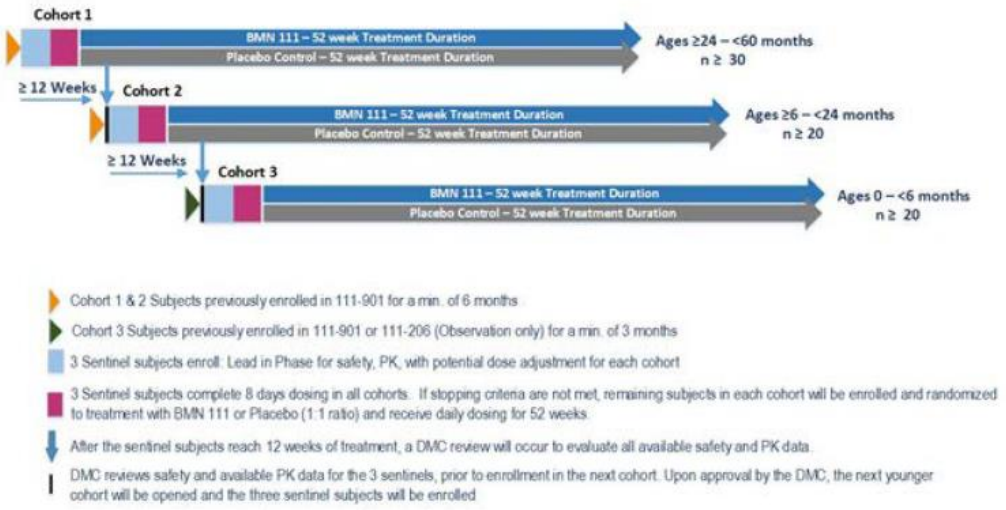
Sentinel subjects from each cohort will be enrolled, treated with vosoritide, and studied for short-term safety and PK data. After the sentinel data are evaluated within a cohort additional recruited subjects will be randomized to receive vosoritide or placebo subcutaneous daily (1:1 ratio) for 52 weeks.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age as follows:

All sentinel and randomized subjects in Cohort 1 received 15 µg/kg dose. Sentinel subjects in Cohort 2 initially received 15 µg/kg dose and the dose was escalated to 30 µg/kg while they remained < 24 months of age following review of PK data as per protocol. All randomized subjects in Cohort 2 will receive 30 µg/kg dose while they remained < 24 months of age. All sentinel and randomized subjects in Cohort 3 received 30 µg/kg dose while they remained < 24 months of age. The dose for all sentinel and randomized subjects in Cohorts 2 and 3 will be adjusted to 15 µg/kg/day after they turn 24 months old.

The 111-206 study design is presented in Figure 4.2.1. All subjects who complete the 111-206 study will be eligible to receive vosoritide in the extension study 111-208 after the Week 52 visit.

Figure 4.2.1: Study Design



4.3 Study Populations

Subjects aged 0 to < 60 months old, with documented ACH confirmed by genetic testing, and who meet the study eligibility criteria will participate.

For additional criteria for selection of study population, please refer to inclusion and exclusion criteria for the protocol.

4.4 Study Dosage and Administration

In Study 111-206, sentinel subjects in Cohort 1 will receive an initial daily dose of 15 µg/kg. All available safety and PK data will be reviewed after 3 sentinel subjects reach Day 8. If the criteria for dose adjustment are met, the 3 sentinel subjects will be started on the new adjusted dose at their next scheduled visit and the remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. The 3 sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment. Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

4.5 Sample Size Determination

Approximately 70 subjects aged 0 to < 60 months at study entry will participate in 111-206. No formal sample size calculations were performed. The number of subjects is considered appropriate to evaluate the safety and efficacy of vosoritide in the target population.

4.6 Blinding and Randomization Methods

4.6.1 Blinding Method

This is a placebo-controlled, double-blind study. Blinding is strictly maintained during the study and a study specific masking plan describes how potentially unblinding data are handled during the lifetime of the study. The study will remain blinded until after all data has been entered, and the final database has been locked.

4.6.2 Randomization Method

The centralized randomization with stratification is managed by an external vendor, using IXRS technology.

Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. In each cohort, eligible subjects will be randomized in a 1:1 ratio to vosoritide or placebo after 3 sentinel subjects are treated. Cohorts 1 and 2 will be stratified by age. Subjects are randomized separately within each cohort in Japan.

4.7 Interim Analysis

No formal interim futility/efficacy analyses are planned. Two informal interim analyses including data from both Studies 111-206 and 111-208 were performed for selected domains: one for New Drug Application (NDA) to Food and Drug Administration (FDA) and marketing authorization applications (MAA) to European Medicines Agency (EMA), dated 18December 2019, and another for Japan New Drug Application (JNDA), dated 11November 2020. For these analyses, subjects remained blinded and no efficacy data was analyzed for the randomized subjects nor post baseline listings except for serious adverse events.

In addition to safety and PK monitoring by BioMarin Personnel, an independent data monitoring committee (DMC) will act in an advisory capacity to BioMarin to monitor subject safety and PK of subjects who participate in the study. A DMC review will occur to evaluate all available safety and PK data after the sentinel subjects complete 12 weeks of dosing, and DMC will make recommendations for stopping or continuing the study, and endorse dose adjustments if needed, based on pre-specified criteria. DMC data review meetings occur approximately every 6 months during the course of the study.

5 GENERAL ANALYSIS CONSIDERATIONS

The analyses described in this final SAP are based on Amendment 2 of the protocol (date: 08 February 2019).

Individual subject data that is reflected in data summaries will be provided in listings. Unless otherwise specified, all listings will be by cohort, by sentinel/randomized subjects, by treatment group, and ordered by subject number, where subject number includes the site number.

Unless otherwise specified, summary tables for efficacy variables will use format in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively. Summary tables for safety variables will be separated by cohort and overall by treatment group using format in Table 5.4.

Table 5.1: Format for Efficacy Summary Analyses for Cohort 1

Sentinel	Randomized						All Vosoritide Treated*		
	Vosoritide			Placebo					
	≥ 24 to < 36 months	≥ 36 to < 60 months	Overall	≥ 24 to < 36 months	≥ 36 to < 60 months	Overall	≥ 24 to < 36 months	≥ 36 to < 60 months	Overall

*All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Table 5.2: Format for Efficacy Summary Analyses for Cohort 2

Sentinel	Randomized						All Vosoritide Treated*		
	Vosoritide			Placebo					
	≥ 6 to < 15 months	≥ 15 to < 24 months	Overall	≥ 6 to < 15 months	≥ 15 to < 24 months	Overall	≥ 6 to < 15 months	≥ 15 to < 24 months	Overall

*All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Table 5.3: Format for Efficacy Summary Analyses for Cohort 3

Sentinel	Randomized		All Vosoritide Treated*
	Vosoritide	Placebo	

*All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Table 5.4: Format for Safety Summary Analyses for Cohort 1*

Sentinel	Randomized		All Vosoritide Treated**
	Vosoritide	Placebo	

* Cohort 2, Cohort 3, and Overall will have the same format as Cohort 1.

**All vosoritide treated includes sentinel subjects and randomized subjects who received vosoritide.

Baseline growth measures (other than AGV, baseline AGV is defined in Section 14.3.2) and baseline weight are those assessed on Day 1 of dosing, regardless of timing relative to dosing. (Note: If no assessments are available, then the baseline assessment will be the last non-missing assessment prior to Day 1). Baseline assessments are the last non-missing on-study assessments prior to administration of study treatment. Change from baseline is calculated as: (post-baseline value – baseline value); Percent change from baseline is calculated as: ([post-baseline value – baseline value]/baseline value) x100.

The screening visit will not be presented in descriptive summaries over time. When the analysis windows have been applied (see Section 5.4), data collected at the screening visit may be included in the baseline assessment. All assessments will be listed, but only those assessments assigned to visits according to the windows applied (see Section 5.4) will be summarized in tables or graphically. Exceptions to this are summaries of the worst post-baseline laboratory data in shift tables where all assessments are considered.

Unless otherwise specified, summary statistics n, mean, standard deviation (SD), median, 25th and 75th percentile, minimum, and maximum will be provided for numerical variables. The mean, 25th percentile, median, 75th percentile, and estimates of precision (e.g. SD, confidence interval) will be displayed to one more decimal place than the collected data. Minimum and maximum values will be presented to the same decimal places as the collected data. The number of decimal places to which endpoints are reported follow the project programming standards.

Number and percentage will be provided for categorical variables. When summarizing categorical data, for mutually exclusive categories, the sum of the individual categories, including a separate “Missing” category, should equal 100%. Unless otherwise specified, if categories have no data, then they will not be displayed.

All statistical analyses will be performed using SAS® version 9.4 or a later release (SAS Institute, North Carolina, USA) and results be presented in the form of tables, listings, and graphs (TLGs). All statistical analyses, including dataset creation and output generation, will

be performed by Biostatistics and Statistical Programming personnel of BioMarin's Biometrics department.

5.1 Analysis Populations

5.1.1 Full Analysis Set

The Full Analysis Set (FAS) is defined according to the intent-to-treat principle and includes all enrolled sentinel and randomized subjects with a signed informed consent. The FAS will be the main analysis population for summaries and/or analyses described in the SAP, including but not limited to summaries and/or analyses of demographics, baseline characteristics, dispositions, and all efficacy endpoints.

All listings, excluding screen failures, will be produced on the FAS.

5.1.2 Per-Protocol

The Per-Protocol (PP) population is defined as a subset of the FAS population who completed the treatment originally allocated (i.e., always received the assigned treatment (vosoritide or placebo)), with a standing height/body length assessment at Week 52 following protocol window, and with treatment compliance of at least 80%.

The PP population will be used for sensitivity analysis of the primary and key secondary efficacy endpoints only.

5.1.3 Safety

The Safety Population is a subset of the FAS who receive at least one dose of vosoritide or placebo in the study. The Safety Population will be used to present the safety summaries by actual treatment received. Subjects randomized to one treatment group, who only receive the study treatment for the other treatment group, will be analyzed in the arm of the study treatment they received.

The Safety Population will be used to present the safety data.

5.1.4 PK

The PK Population is defined as all sentinel subjects and subjects randomized to vosoritide treatment group, who received at least one dose of vosoritide in this study and have at least one evaluable PK concentration.

5.1.5 Immunogenicity

The Immunogenicity Population is defined as all subjects in the Safety Population who have at least one evaluable immunogenicity sample. Subjects randomized to one treatment group, who only receive the study treatment for the other treatment group, will be analyzed in the arm of the study treatment they received.

5.2 Pooling of Data from Sites with Small Enrollment

Not applicable, as there are no analyses by site.

5.3 Study Day Derivation

Study day in 111-206 will be determined by subtracting the initial study treatment start date from a visit date plus 1 if the visit date occurs on or after the initial study treatment start date. Otherwise, the study day will be the visit date minus the initial study treatment start date. Therefore, Study Day 1 will occur on the initial study treatment start date. i.e.

- Study Day 1 = Day of first dose of study treatment.
- If Visit Date < Study Treatment Start Date, then Study Day = Visit Date - Study Treatment Start Date
- If Visit Date >= Study Treatment Start Date, then Study Day = Visit Date - Study Treatment Start Date +1

5.4 Visit Windows for Analysis

An assessment for a subject will be classified according to the study day of the assessment where it falls within a window.

Observational data in 111-901 for subjects who enrolled in 111-206 and are included in the corresponding analysis population will be used in efficacy summary tables and figures. For Cohort 3 subjects, data from the observational period in 111-901 or 111-206 will be included. The analysis visits and windows for observational assessments in 111-901 and 111-206 are defined in Table 5.4.1. Unless otherwise specified, only the derived visits listed in the table will be included in summary tables and figures.

Table 5.4.1: Visit Windows for Observed Assessments in BMN 111-901 and BMN 111-206

Derived Visit	Target Day[a]	Analysis Window[a]
3 Months Prior in 111-206 or 111-901 for Cohort 3 subjects*	-91	target day +/- 42 days
6 Months Prior in 111-901*	-182	target day +/- 42 days

[a] Target days and analysis windows are relative to the 111-206 Day 1 date defined in Section 5.3 above.

* In the event a subject does not have an assessment in the 3 months prior or 6 months prior window then the closest assessment to the target date will be considered. If the two closest assessments to the target day are equidistant from the target day, the latest assessment will be used.

For each subject and growth measure in study 111-901, the record closest to the target day within the analysis window will be retained for inclusion in summary tables.

Spaghetti plots of standing height/body length Z-Score will include measures every 6 months recorded and including the "6 months prior", "3 months prior" for subjects in Cohort 3 from Study 111-901 or 111-206. This will allow for all subjects with height assessments 3 months prior to Day 1 to have at least one assessment included.

The analysis windows for assessments in 111-206 are defined in Table 5.4.2. The analysis windows are designated to be consecutive for scheduled visits to accommodate delayed visits due to impact of COVID-19. The upper bound of each visit window will be target day plus half of the difference between the current target day and the next target day, and the lower bounds of the window will be the upper bound of the previous window plus 1 except for Day 1, Day 2, Day 3, and Week 52. Lower bound, upper bound, and target date are the same for Day 1, Day 2, and Day 3. The upper bound of Week 52 will be target day plus 42 days. If there are two or more assessments within a designated window, the assessment that is closest to the target day will be used for analyses. If the two closest assessments to the target day are equidistant from the target day, the assessments taken on a scheduled visit per case report form (CRF) page will be used; if both are scheduled visits but not on the same day, the latest assessments will be used; if both are on the same day, the average of the assessments will be used. Unless otherwise specified, all analyses are based on derived visits.

Table 5.4.2: Visit Windows for Observed Assessments in 111-206

Derived Visit	Target Day[a]	Analysis Window[a]
Baseline		The last assessment prior to the first dose of study treatment unless otherwise specified.
Day 1	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 8	Day 8	Day 4 - 15
Week 3	Day 22	Day 16 - 33
Week 6	Day 43	Day 34 - 68
Week 13	Day 92	Day 69 -117
Week 20	Day 141	Day 118 - 162
Week 26	Day 183	Day 163 - 229
Week 39	Day 274	Day 230 - 320
Week 52	Day 365	Day 321 - 407

[a] Target days and analysis windows are relative to Day 1 date defined in Section 5.3.

5.5 Handling of Dropouts and Missing Data

For descriptive summaries, missing data will not be imputed. For model-based analyses, an imputation will be conducted for endpoints missed at Week 52. Detailed imputation rules are described in Section 14.1.

Other than for partial/missing dates described below, there will be no imputation for safety data.

5.5.1 Partial Dates

Where start and stop dates for medications or adverse events are incomplete, imputation rules will be applied.

In the event that the start date of a medication/AE is partial, the following imputation rules will be applied:

- If only day is missing, then the start date will be imputed as the first day of the month. If month and year are the same as the month and year of first dose of study treatment, then the start date will be imputed as the first dose date in the study in which the AE occurred.

- If only year is non-missing, then the start date will be imputed as the first day of the year. If year is the same as the year of first dose of study treatment, then the start date will be imputed as the first dose date in the study in which the AE occurred.

In the event that the stop date of a medication/AE is partial, the following imputation rules will be applied:

- If only day is missing, then the end date will be imputed as the last day of the month.
- If only year is non-missing, then the end date will be imputed as the last day of the year. If the imputed date is beyond the study completed or discontinued date of the study in which the AE occurred, the imputed date will be replaced with the study completed or discontinued date.

6 SUBJECT DISPOSITION

Disposition will be presented based on the FAS. The number of subjects enrolled/randomized, the number of subjects who received study treatment, the number of subjects who completed study treatment, and the number of subjects who completed the study will be reported separately by cohort and overall by treatment group using format as specified in Table 5.4.

Disposition data will be listed for both the sentinels and randomized subjects by cohort and treatment group, and will indicate the investigator site. In addition, a listing will be provided for those subjects who were screen failures, along with the reason for screen failure.

7 DISCONTINUATION AND COMPLETION

For subjects who prematurely discontinued from the study, the primary reason for discontinuation will be summarized. A similar summary will be provided for subjects who discontinued study treatment.

The number of subjects who completed study treatment and the number of subjects who completed the study will be summarized by cohort and overall by treatment group using format as specified in Table 5.4. All summaries will be based on the FAS.

Listing will be provided on the FAS.

8 PROTOCOL EXEMPTIONS AND DEVIATIONS

The number and percentage of subjects with any protocol deviation, any major protocol deviation, and any minor protocol deviation will be presented separately by cohort and overall by treatment group using format as specified in Table 5.4, according to the categories described in the study specific protocol deviation plan. Reasons for major/minor deviations will be summarized. Subjects who received the wrong treatment will be identified after data base lock and considered as a Major Protocol Deviation.

All summaries will be based on the FAS.

All protocol deviations will be listed for sentinel and randomized subjects by cohort. sentinel/randomized subjects, treatment group, and subject ID. A separate listing of all major deviations which have been classified as a “Dosing Irregularity” will also be provided.

In addition, a summary and listing of COVID-19 specific protocol deviations will be provided.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for the FAS, and presented for by cohort by treatment group with the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively and Table 5.4 for Overall. Rules on standing height/body length and sitting height/crown to rump length are provided in Section 14.1.

Demographics will be summarized as:

- Age at Screening (months with 1 decimal place)
- Age at Day 1 (months with 1 decimal place)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian [Japanese/Other], Black or African American, Native Hawaiian or Pacific Islander, White, Multiple, Not Provided Due to Patient Privacy Rules)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Baseline characteristics will be summarized as:

- Weight (kg) and Weight Z-Score
- Body Mass Index (BMI) (kg/m^2), and also BMI Z-Score for subjects aged 24 months or older

Baseline growth measures will be summarized as:

- Height Z-Score (Refer to Section 14.2.1)
- AGV (cm/yr)
- Standing Height/Body Length (cm)
- Sitting Height/Crown to Rump(cm)
- Lower Body Length (cm) = Standing Height - Sitting Height
- Head Circumference (cm)
- Upper Arm Length (cm)
- Lower Arm (Forearm) Length (cm)
- Arm Span (cm)
- Upper Leg Length (Thigh) (cm)
- Knee to Foot Height (cm)

- Tibial Length (cm)
- Upper to Lower Body Segment Ratio
- Arm Span to Standing Height Ratio
- Upper Arm Length to Lower Arm (Forearm) Length Ratio
- Upper Leg Length to Tibial Length Ratio

A listing of each sentinel and randomized subject's demographic/baseline data will be provided.

10 MEDICAL HISTORY

Medical history will be solicited from each subject, including all major illnesses, diagnoses, and surgeries that the subject has ever had; any prior or existing medical conditions that might interfere with study participation or safety; and evaluation for knee, thigh, hip or groin pain, or change in gait/activity.

All medical history terms will be coded in accordance with MedDRA Version 24.1 that each term is assigned a SOC and PT.

A list of PTs considered to be ACH-related will be reviewed prior to the data cut. A listing for the complete list of final terms will be generated, retained in the study file, and documented in the CSR.

All recorded medical history will be summarized on the FAS by SOC and by PT by cohort and overall by treatment group using format as specified in Table 5.4, ordered by descending order of frequency of SOC in the overall population. In addition, achondroplasia-related medical history will be listed and summarized separately by SOC and PT in a similar manner.

The number of subjects with abnormal physical exam results at screening will be summarized and listed.

A listing of each subject's medical history will be provided, plus a listing of each subject's achondroplasia-related medical history.

11 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be summarized for the FAS. For analysis purposes, the following definitions will be used to determine prior and concomitant medications for the entire study period:

- Prior medications: Any medications taken and ended prior to the initial study treatment administration date will be considered prior medications.
- Concomitant medications: Any medications taken on or after the initial study treatment administration date up to 30 days after discontinuation of study treatment will be considered concomitant medications and included in summary tables. This also includes medications initially taken prior to the initial study treatment administration date but continued or ended on or after the initial study treatment administration date.

Concomitant medications will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4, and a separate summary will be provided which includes only those concomitant medications that were initiated on study.

All medications will be coded using the latest version available within BioMarin of the World Health Organization Drug (WHO Drug) dictionary (Version September 2021). Prior and concomitant medication use will be separately summarized by Anatomical Therapeutic Chemical (ATC) medication class (Level 2) and preferred name (i.e., generic medication name). If a medication doesn't have ATC level 2, they are grouped as "ATC Level 2 classification unavailable". A subject reporting the same medication more than once will be counted once when calculating the number and percentage of subjects who received that medication. A listing of prior and concomitant medications will be provided. In addition, a listing for COVID vaccine will be provided.

12 COMPLIANCE

Treatment compliance will be calculated based on the study treatment preparation and study treatment administration records captured in the eCRF, and summarized separately by cohort and overall by treatment group using format as specified in Table 5.4 for the safety population.

For each subject it considers all data up to the last recorded dose. For each column, results will be separated for 15 µg/kg, 30 µg/kg, and overall.

For each daily injection, the amount of study treatment taken will be calculated based on the number of units in the syringe pre-injection, minus the number of units remaining in the syringe post-injection. For the cases that the number of units in the syringe pre-injection is not captured in the eCRF, if response to "Was study drug administrated?" is "Yes", then it will be assumed to be the same as the planned dose; if response to "Was study drug administrated?" is "No", then it will be assumed to be missing and these records will not be included in the compliance calculation.

The total amount of study treatment taken will be calculated based on the amount of study treatment taken (units) in the corresponding treatment duration.

The total amount of study treatment planned is determined based on the duration of treatment and the planned dose per day.

Percentage compliance for each subject will be derived from the total amount of study treatment intake divided by the planned study treatment intake, and multiplied by 100:

$$\text{Treatment Compliance (\%)} = \frac{Total\ Amount\ of\ Study\ Drug\ Taken\ (units)}{Total\ Amount\ of\ Study\ Drug\ Planned\ (units)} \text{ x } 100$$

Treatment compliance will be calculated and summarized separately by cohort and overall by treatment group using format as specified in Table 5.4. For each column, results will be separated for 15 µg/kg, 30 µg/kg, and overall.

- Compliance with protocol-specified treatment regimen (%)
- Compliance with protocol-specified treatment regimen (≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥100%, >=110%, >=120%)

Listings will be provided for compliance.

13 EXTENT OF EXPOSURE TO STUDY TREATMENT

Dosing information is recorded by subjects in the paper diary and also by the site on visit days. In the case of duplicate records with the same date, if the investigator confirms the date, then investigator reported dosing data will be used. All summaries will be produced based on the safety population, and presented separately by cohort and overall by treatment group using format as specified in Table 5.4. For each column, results will be separated for 15 µg/kg, 30 µg/kg, and overall.

Descriptive statistics will be provided for the following variables:

- Duration of treatment (days)

  = Date of last dose – Date of first dose + 1
- Total number of doses administered

  = Number of doses administered between date of Day 1 and date of last dose
- Total number of doses missed

  = Number of doses missed between date of Day 1 and date of last dose
- Total amount of weight adjusted dose administered (µg/kg) by planned dose
- Average weight-adjusted daily dose administered (µg/kg/day) by planned dose

The frequency and percent of subjects will be provided for the following variables, where missed doses are counted between the date of first dose (Day 1) and date of last dose:

- Number of subjects who missed at least one dose
- Number of subjects who missed more than one dose
- Number of subjects who missed more than 5 consecutive doses
- Number of subjects who missed more than 10 consecutive doses

The frequency and percent of events will be provided overall for the following variable:

- The total number of missed doses and reason for each missed dose (Site Error, Parent/Caregiver Error, Home Health Error, Adverse Event, Other, Missing) will be provided.

A listing of each subject's extent of exposure by planned dose 15 µg/kg and 30 µg/kg will also be provided.

14 EFFICACY EVALUATIONS

14.1 General Approaches for Analyzing Growth Parameters

All growth parameters assessed by anthropometric measurements are measured at Baseline, Day 1, Week 6, Week 13, Week 26, Week 39, Week 52, and early termination visit.

Growth parameters are measured 3 times for each assessment. It is the mean of these 3 assessments that are considered for the summaries and analyses. In the event that all 3 are not available, the mean of the 2, or the individual assessment is taken. All measures and means of the measures will be included in the listings.

The general rule when summarizing height (standing and sitting) is that standing height/sitting height will be used if subjects ≥ 24 months, body length/crown to rump will be used if subjects < 24 months. For subjects with both sets of measurements available, like to like will be used based on their measurements available for their age at baseline.

Thus, in general, for subjects in Cohort 1 standing height and sitting height will be summarized. For subjects in Cohorts 2 and 3 body length and crown to rump will be summarized. If body length is not measured and standing height is available, standing height will be used. If both sets of measures are available, like to like will be used based on their measurements available for their age at baseline.

These rules will impact the following growth endpoints: standing height/body length Z-Score, standing height/body length, AGV, sitting height/crown to rump, lower body length, arm span to height ratio, upper to lower body segment ratio, BMI, and BMI Z-Score.

BMI Z-Score will only be derived for subjects aged 24 months or older.

Body length and crown to rump will not be summarized separately but integrated within the summaries for standing height and sitting height. Body length and crown to rump are however provided separately in a listing.

Appendix 25.1 provides details of the derivations used for each endpoint.

All efficacy endpoints will be assessed using the FAS.

Visit windows are applied for all assessments (see Section 5.4) and are used to summarize the growth measures by visit.

All parameter assessments are considered for inclusion in analyses.

With the exception of AGV (see Section 14.3.2), summary tables for all growth measures including standing height/body length Z-Score, standing height/body length, upper to lower body segment ratio, body proportion ratios, other growth measures (see Section 14.3.5), BMI, BMI Z-Scores, and weight Z-Scores will include assessments at baseline, Week 26 and Week 52 from Study 111-206, and 6 months prior in Study 111-901. For subjects in Cohort 3 assessments at 3 months prior to baseline in Studies 111-206 or 111-901 will be included.

Each table will include summaries of the absolute observed measures and its change from baseline at each of these time points. The tables will summarize data separately by cohort by treatment group using format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

ANCOVA models will be conducted for change from baseline at Week 52 in standing height/body length Z-Score, standing height/body length, AGV, and upper to lower body ratio for all cohorts overall and/or by cohort, as appropriate. Unless otherwise specified, all models will include the following baseline covariates: randomization age stratum, age at baseline, baseline AGV, and sex. Analyses of standing height/body length Z-Score, standing height/body length, and upper to lower body ratio will include their baseline as additional covariate.

For the model-based analyses, if the required assessment at Week 52 is missing but there are assessments before and after Week 52, a linear interpolation using the measurements closest to the before and after Week 52 will be used, otherwise those with no assessment after Week 52, multiple imputation by using placebo data from subjects in the same cohort (PROC MI) will be used to impute the missing values for standing height/body length and upper to lower body segment ratio at Week 52.

In addition to the primary analyses conducted on FAS, sensitivity analyses will also be conducted and are described in Section 14.2.

Results of the statistical analyses will be provided in separate tables, including the least-squares (LS) mean change from baseline at Week 52 for each treatment group, the treatment difference in LS means (calculated as vosoritide - Placebo), the 95% confidence interval (CI) for the treatment difference, and corresponding 2-sided p-value.

Listings for standing height/body length and standing height/body length z-score will include all assessments (i.e., all measures and means of the measures) and spaghetti plots for height and height Z-Score will include assessments every 6 months and will be ordered by cohort,

sentinel/randomized subject, treatment, subject ID and visit date including 111-901 and 111-206.

14.2 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in standing height/body length Z-Score at Week 52.

Each measurement of derived standing height/body length will be converted to an age-and sex-appropriate standard deviation score (SDS), also referred to as a Z-Score, by comparison with reference data available for average stature children from the CDC. Note no data conversions are applied between body length and standing height as recommended for average stature.

Standing height/body length Z-Scores will be derived using CDC references and macro (CDC, 2019).

14.2.1 Primary Analyses

The standing height/body length Z-Score at 6 Months Prior to baseline, 3 Months Prior to baseline for Cohort 3, baseline, Week 26 and Week 52, and it's change from baseline at Week 26 and Week 52 will be summarized and presented separately by cohort by treatment group using format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

Height Z-Scores derived for all visits from 111-901 and 111-206 will be included in data listings.

A line plot of individual standing height/body length Z-Score will be presented at baseline and Week 52 for each subject by cohort by stratified age stratum. A line plot of the mean (+/-SD) standing height/body length Z-Score will be presented by cohort at 6 Months Prior (3-month prior for Subjects in Cohort 3), Baseline, Week 26 and Week 52.

For the model-based ANCOVA analyses, estimand formulation is as follows:

- Population: All randomized subjects in FAS overall and/or by cohort as appropriate
- Variable: Change from baseline in standing height/body length Z-Score at Week 52
- Intercurrent event: Regardless of whether or not switching to rescue medication had occurred or subjects had discontinued from the treatment. See Section 14.1 for handling of missing data
- Population-level summary: Lsmean difference and 95%CI between the treatment groups based on ANCOVA models defined in Section 14.1

ANCOVA model will include the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where baseline covariates include randomization age stratum, age at baseline, sex, baseline AGV, and baseline height Z-Score. The following SAS Proc Mixed with option OBSMARGINS for lsmeans will be used to perform the analysis on all randomized subjects in FAS overall and/or by cohort by each imputed dataset:

```
PROC MIXED;
CLASS Treatment Sex Age_stratum;
MODEL Change from baseline in height Z-Score at Week 52 = Treatment
Age_baseline Sex Age_stratum AGV_baseline Height Z-Score_baseline;
LSMEANS Treatment / DIFF CL OM;
ESTIMATE 'Active - Placebo' Treatment 1 -1/CL;
RUN;
```

For the models that will include the data from the multiple imputation a “by imputation statement will be included” and then PROC MIANALYZE will be used to combine the estimates from each of the mixed models.

These analyses will be repeated by also including sentinel subjects from the corresponding cohort.

14.2.2 Sensitivity Analyses

The following sensitivity analyses will be conducted on the primary efficacy endpoint:

(1) Model-based analyses on the subjects in the PP population

(2) Model-based analyses on the subjects with no missing data at Week 52

14.3 Secondary Efficacy Endpoint(s)

14.3.1 Standing Height/Body Length

Rules for standing height/body length is described in Section 14.1.

The standing height/body length and its change from baseline will be summarized and presented separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

Standing height/body length will be analyzed using the same methods and estimand formulation as the primary efficacy endpoint analysis and sensitivity analyses. An analysis of change from baseline in standing height/body length at Week 52 will be performed using an

ANCOVA model that includes the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where baseline covariates include randomization age stratum, age at baseline, sex, baseline AGV, and baseline standing height/body length.

Standing height/body length for all visits will be included in data listings including data from 111-901 and 111-206.

Spaghetti plots of standing height/body length at every 6 months assessments including height assessments collected in the 111-901 study (3-month prior for Subjects in Cohort 3) will be provided for each subject separately by cohort. This plot will include age-sex specific reference ranges for average stature children (from CDC, 2019) and age-sex specific reference ranges for short stature children (Hoover-Fong, 2021).

For these plots if body length is used for Cohort 1, it will be indicated in the plot. Likewise, if standing height is used for Cohort 2, it will be indicated in the plot.

A line plot of the mean (+/-SD) standing height/body length will be presented by cohort at 6 Months Prior (3-month prior for Subjects in Cohort 3), Baseline, Week 26 and Week 52.

14.3.2 Annualized Growth Velocity

For a given interval [Date1, Date2], the AGV is defined as follows:

AGV (cm/yr) = (Derived Standing Height at Date 2-Derived Standing Height at Date 1)/(Interval Length (Days)) x 365.25

where the interval length in days is calculated as Date2 - Date1.

AGV (cm/yr) will be calculated at baseline, Week 26, and Week 52. AGV at baseline will be calculated by using height measurements in Study 111-901 6 months prior to Day 1 of Study 111-206 for subjects in Cohorts 1 and 2, and using height measures in Study 111-901 or 111-206 3 months prior to Day 1 of Study 111-206 for subjects in Cohort 3. AGV at other time points will be calculated cumulatively from Day 1 of 111-206 and every 6 months interval.

The absolute values for cumulative AGV and 6-month AGV and their change from baseline will be summarized and presented separately by cohort by treatment group using the format specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

Cumulative AGV will be analyzed using the same methods and estimand formulation as the primary efficacy endpoint analysis and sensitivity analyses. An analysis of change from baseline in cumulative AGV at Week 52 will be performed using an ANCOVA that includes the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where

baseline covariates include randomization age stratum, age at baseline, sex, and baseline AGV.

A box and whisker plot will be provided for AGV (cm/yr) over time by cohort and treatment group. A line plot of individual cumulative AGV will be presented at baseline and Week 52 for each subject by cohort by stratified age stratum.

Listings for the cumulative AGV and 6 months AGV will include all calculated AGV.

14.3.3 Upper to Lower Body Segment Ratio

The upper to lower body segment ratio will be calculated at each visit as follows:

$$\text{Upper to Lower Body Segment Ratio} = \frac{Derived\ Sitting\ height(cm)}{Derived\ Standing\ height(cm) - derived\ Sitting\ height(cm)}.$$

The ratio of derived sitting height and derived standing height will also be calculated.

The upper to lower body segment ratio, the sitting to standing height ratio, and their change from baseline will be summarized and presented separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

Upper to lower body segment ratio will be analyzed using the same methods and estimand formulation as the primary efficacy endpoint analysis and sensitivity analyses, an analysis of change from baseline in the upper to lower body segment ratio at Week 52 will be performed using an ANCOVA model that includes the fixed-effects of treatment (active arm vs. placebo arm) and baseline covariates, where baseline covariates include randomization age stratum, age at baseline, sex, baseline AGV, and baseline upper to lower body segment ratio.

Upper to lower body segment ratio and sitting to standing height ratio derived for all visits will be included in data listings including data from 111-901 and 111-206.

A line plot of individual upper to lower body segment ratio will be presented at baseline and Week 52 for each subject by cohort by stratified age stratum. A line plot of the mean (+/-SD) upper to lower body segment ratio will be presented by cohort at 6 Months Prior (3-month prior for Subjects in Cohort 3), Baseline, Week 26 and Week 52.

14.3.4 Body Proportion Ratios

Body proportion ratios include:

- Upper Arm Length to Lower Arm (Forearm) Length Ratio
- Upper Leg Length (Thigh) to Knee to Heel Length Ratio

- Upper Leg Length (Thigh) to Tibial Length Ratio
- Arm Span to Standing Height Ratio

The absolute values and its change from baseline will be summarized and presented separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

All assessments will be listed.

14.3.5 Other Growth Measures

Other growth measures include:

- Sitting Height (cm)/Crown to Rump (cm)
- Upper Leg Length (Thigh) (cm)
- Lower Leg Length: Knee to Foot (cm)
- Lower Leg Length: Tibia Length (cm)
- Head Circumference (cm)
- Upper Arm Length (cm)
- Lower Arm (Forearm) Length (cm)
- Arm Span (cm)

In addition, derived standing height and derived sitting height will be calculated as specified in Section 14.1, and a measure of lower body length will be calculated as follows:

- Lower Body Length (cm) = Derived Standing height – Derived Sitting height

Baseline growth measures are those assessed on Day 1, regardless of timing relative to dosing. All summaries and analyses will be based on the FAS.

For each of the above growth measures (including lower body length), the absolute values and its change from baseline will be summarized and presented by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

All assessments will be listed by subject and visit.

14.4 Health-Related Quality of Life

The Health-Related Quality of Life (HRQoL) questionnaires and functional independence questionnaires are captured at Baseline, Week 26, Week 52. All summaries will be generated on the FAS.

Each table will include summaries of the absolute measures at each of these time points and change from baseline at every 26 weeks. The tables will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

The statistical summaries will include the number of subjects with assessable data, mean, SD, median, 25th and 75th percentile, minimum and maximum. Subjects will not be included in a summary table if there is no baseline assessment available.

Separate summary tables will be provided for the total summary scores and the individual domains (scales). Individual questions (items) are not included in the summary tables.

Age-defined versions within the same questionnaire will be summarized together. If subjects progress during the course of the study from one age-defined questionnaire to the next age-defined questionnaire the results will be summarized together and the baseline assessment from the child's first questionnaire is referred to when summarizing change from baseline.

If a questionnaire for the wrong age group was filled, outcomes will not be included in the summary table but will be included in the listings.

Self-reports and parent-reports will be summarized separately but together in the bat charts.

All subject data listings will include total scores, and domain (scale) scores.

14.4.1 Bayley-III

The Bayley-III is a performance-based outcome assessment for use in children from 1 to 42 months.

Scales include Cognitive scale, Language (Receptive Communication and Expressive Communication subscales) scale, and Motor (Gross and Fine Motor subscales) scales.

In addition to its use for subjects ranging from 1 to 42 months old, the Bayley-III assessment will be administered to those entering the study between 42 and 60 months old and for the remainder of the duration of this study, as this assessment can capture ongoing developmental issues associated with ACH. Bayley-III is waived for subjects < 1 month old.

Scales/Subscales:

- Cognitive
- Language
    - Receptive Communication
    - Expressive Communication

- Motor
    - Fine Motor
    - Gross Motor

Each (sub)scale yields a total raw score which is then standardized according to the subject's chronological age (scaled scores).

Scoring

Number of items depends on which set is given in each domain. The number of questions administered depends in part on the child's age and on their developmental level.

The total raw scores for the Cognitive Scale and the Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor subscale are the sums of the number of points earned for a (sub)scale.

The raw scores cannot be accurately compared to each other as each subscale has a different number of items resulting in a different range of possible scores. Therefore, the comparisons are best based on derived scores: age-based scaled scores or composite scores[8].

Scaled scores represent a child's performance on a (sub)scale relative to the same age peers. They are derived from the total raw scores on each of the subscale and are scaled to a metric with a range of 1 to 19, a mean of 10 and a SD of 3.

Composite scores are scaled to a metric with a mean of 100 and a SD of 15, and range from 40–160.

For the Language and Motor Scale, composite scores are derived from the sums of age-corrected scaled scores. For each composite, the distribution of the sum of scaled scores is used to derive corresponding percentiles which are converted to composite scores with a mean of 100 and a standard deviation of 15.

For the Cognitive subdomain the scaled score to composite equivalent is a linear conversion from one scale (mean=10, SD=3) to another (mean=100, SD=15).

For the scaled scores and composite scores, the absolute values will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

The 3 composite scores (Cognitive, Language and Motor) will be displayed by cohort and treatment group in a bar chart.

14.4.2 Infant and Toddler Quality of Life Questionnaire (itqol-97, 2013) (ITQOL)

The Infant Toddler Quality of Life questionnaire (ITQOL) is an observer-reported outcome tool developed for use in children from 2 months to 5 years old that attempts to capture physical, mental and social well-being. The ITQOL adopts the World Health Organization's definition of health as a state of complete physical, mental and social well-being, and not merely the absence of disease. The ITQOL also assesses the quality of the parents/guardians' life. The 97-item full-length version (ITQOL) will be used for this study. ITQOL is waived for subjects < 2 months old.

Domains

The following domains are part of the ITQoL:

- Overall Health (1item)
- Physical abilities (10 items)
- Growth and development (10 items)
- Pain (3 items)
- Temperament and mood (18 items)
- Behavior (12 items)
- Global behavior (1 items)
- Getting on with others (15 items)
- Global health perceptions (11 items)
- Change in health (1 item)
- Parental impact emotional (7 items)
- Parental impact time (7 items)
- Family cohesion (1 item)

For the ITQOL, the exact number of items that can be missing differs depending on which section is being scored, though the general rule is that a section can be scored if at least half the responses in that section were completed.

Summary scores for the 13 domains (overall score) will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

The summary scores for Overall Health, Physical Abilities and Growth and Development will be displayed separately for the sentinel and randomized subjects by cohort and treatment group in a bar chart.

14.4.3 Function Independence Measure (WeeFIM) (Wee-FIM II Version 6.4)

The WeeFIM (Functional Independence Measure for children) instrument is a functional independence assessment tool that measures functional performance across three domains (self-care, mobility and cognition) from the caregiver's perspective.

Performance of a child on each of the individual items within the WeeFIM is assigned to one of seven levels on an ordinal scale that represent the function from complete and modified independence (levels 7 and 6) without a helping person to modified and complete dependence (levels 5 to 1) with a helping person.

If individual items (questions) within a domain are missing, the item result is imputed to 1, per guidance in The WeeFIM Clinical Guide v 6.49.

If all items for a domain score are missing the domain score is considered missing.

If a domain score is missing, the Total score is missing.

For each of the following domains and the total score, the absolute values at each scheduled visit, and change from baseline at each scheduled visit, will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively:

- Self-care Score (min score=8, max score=56)
- Mobility Score (min score=5, max score =35)
- Cognition Score (min score=5, max score=35)
- Total WeeFIM rating (min=18, max=126)

Domain and total scores will be listed by cohort, sentinel/randomized subjects, treatment group, and subject number.

Note: Although each domain will be summarized so that all aspects of this validated scale are reported, the cognition aspect of the WeeFIM (cognition subtotal score) is considered not to be of concern for subjects with achondroplasia.

The three domains and Total WeeFIM score will also be displayed by visit in a bar chart and presented separately for the sentinel and randomized subjects by cohort and treatment group.

14.5 Sleep Study Scores

A sleep study will be performed in a limited number of qualified sleep centers. A sleep-testing device will be used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea will include, but may not be limited to, the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index). Sleep study data is collected at Screening, Week 52, and early termination visit.

Following episodes of sleep apnea variables will be summarized separately by cohort by treatment group using the format as specified in Table 5.1, Table 5.2, and Table 5.3 for Cohorts 1, 2, and 3, respectively.

- Number of episodes of apnea per hour (Apnea Index).
- Number of episodes of hypopnea per hour (Hypopnea Index).
- Number of episodes of obstructive apnea hypopneas per hour (Apnea Hypopnea Index)
- Number of episodes of obstructive apneas per hour (Obstructive Apnea Index)
- Number of episodes of central apneas per hour (Central Apneas Index)
- Number of desaturations per hour ≥ 3%

Listing of the above episode of sleep apnea variables will be provided.

15 SAFETY EVALUATIONS

The safety population will be used for all safety summaries.

Summary tables assessing safety parameters at planned visits over time will include all safety events up to 30 days following treatment discontinuation. These summary tables will be presented separately by cohort and overall by treatment group using format as specified in Table 5.4. Listings will include all reported data.

Safety will be assessed by examining the incidence, frequency, severity (determined using the CTCAE version 4.03), and relationship to study treatment of all TEAEs reported during the study period. In addition, changes from baseline in clinical laboratory results and vital signs will be assessed.

15.1 Adverse Events

Adverse events (AEs) will be coded in accordance with MedDRA Version 24.1 and performed prior to DBL. Coding of the severity of AEs is performed by the investigators using national cancer institute (NCI) CTCAE version 4.03, where events are coded from CTCAE Grade 1 to Grade 5.

Only TEAEs defined as any adverse event that newly appeared, increased in frequency, or worsened in severity following initiation of study treatment administration are reported by the investigators and consequently are included in the summary tables.

In the event that the start date of an AE is incomplete or missing, conservative imputation rules are applied so that where there is uncertainty, the event is considered treatment emergent. Similarly, the AE end dates are imputed in a conservative manner to a maximum length.

15.1.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4. In summaries by SOC and/or PT, subjects with more than one AE of the same SOC or PT will be counted once within that SOC/PT. For those AEs that occurred more than once during the study, AEs by severity will be summarized by the maximum CTCAE grade and by all CTCAE grades. The tables are ordered by the descending frequency of SOC or PT of overall in the table.

The following summary tables will be provided:

- Overview of the incidence of TEAEs
- Overview of exposure-adjusted event rates of TEAEs
- Incidence and exposure-adjusted event rates of TEAEs by SOC, PT, and CTCAE grade
- Incidence of TEAEs by SOC, PT and highest CTCAE grade
- Incidence of and exposure-adjusted event rates TEAEs by PT
- Incidence of TEAEs by SOC
- Incidence of and exposure-adjusted event rates treatment related TEAEs by SOC, PT and CTCAE grade
- Incidence of and exposure-adjusted event rates TEAEs with CTCAE Grade >= 3 by SOC, PT and CTCAE grade
- Incidence of serious adverse events (SAEs) by SOC and PT
- Incidence of non-serious adverse events by SOC and PT
- Incidence of TEAEs leading to study or study treatment discontinuation by PT
- Incidence of TEAEs leading to study treatment interruption by PT
- Incidence of TEAEs leading to study treatment dose reduction by PT
- Incidence of achondroplasia related TEAEs by SOC and PT*

* Achondroplasia-related TEAEs will be identified using the PTs identified for achondroplasia-related medical history (see Section 10). In addition, all AEs will be reviewed prior to DBL and the list updated as required.

For exposure-adjusted event rates of TEAEs, exposure will be derived to up to the last dose reported in the study database.

Listings:

In addition to the above tables, the following listings will be provided and ordered by subject and AE start date:

- All TEAEs
- TEAEs with CTCAE Grade ≥ 3
- Achondroplasia-related TEAEs
- SAEs
- Deaths

- TEAEs leading to study or study treatment discontinuation
- TEAEs leading to study treatment interruption or dose reduction
- TEAEs of confirmed/suspected COVID-19
- TEAEs occurring within 14 days following COVID-19 Vaccine

15.1.2 Events of Interest

Events of interest (EOI) will be summarized by PT separately by cohort and overall by treatment group using format as specified in Table 5.4. For those AEs that occurred more than once during the study, the maximum severity will be used to summarize the AEs by severity.

The following are identified as events of interest:

Injection site reactions (ISR)

- TEAEs with a MedDRA High Level Term (HLT) of "Injection site reaction".

Hypotension

- TEAEs with PT: Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure orthostatic decreased, Blood pressure systolic decreased, Blood pressure systolic inspiratory decreased, Diastolic hypotension, Hypotension, Orthostatic hypotension.

Heart rate change

- TEAEs with a PT: Atrial tachycardia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Sinus tachycardia, Supraventricular tachycardia, Tachycardia, Tachycardia paroxysmal, Ventricular tachycardia, Bradycardia.

Hypersensitivity SMQ

- TEAEs with a PT included in the MedDRA hypersensitivity SMQ

Algorithmic Anaphylaxis SMQ (with sponsor-defined time restrictions)

- TEAEs with a PT included in the MedDRA anaphylactic reaction SMQ, with an additional time restriction: a narrow scope PT within 48 hours of a dose, or two broad scope PTs from different classes where both PTs are within 48 hours of the same dose.

Fractures

- TEAEs with a PT containing the term "fracture" and also PTs of Bone fragmentation, Bone fissure, Scapulothoracic dissociation and Flail chest

Slipped Capital Femoral Epiphysis (SCFE)

- TEAEs with a PT: Epiphyseal disorder, Epiphyseal injury

Avascular necrosis and osteonecrosis

- TEAEs with a PT: Osteonecrosis, Osteonecrosis of jaw, Osteonecrosis of external auditory canal, Necrosis ischaemic

Events of interest will be summarized as follows:

- Incidence and exposure-adjusted event rates of ISR events by PT
- Incidence and exposure-adjusted event rates of hypotension by PT
- Incidence and exposure-adjusted event rates of heart rate change events by PT
- Incidence and exposure-adjusted event rates of hypersensitivity (SMQ)
- Profile of ISRs
- Profile of hypotension
- Profile of heart rate change events

Profile summaries include: highest CTCAE grade, number of events per subject, time from first dose to first event onset, duration of events (days), action taken with study treatment, outcome of events.

Listings:

In addition to the above tables the following EOI listings are also provided:

- TEAEs of injection site reaction
- TEAEs of hypotension
- TEAEs of documented symptomatic hypotension
- TEAEs of heart rate change events
- TEAEs of hypersensitivity (SMQ)
- TEAEs of algorithmic anaphylaxis (SMQ) with sponsor-defined time restrictions
- TEAEs of fractures
- TEAEs of SCFE
- TEAEs of avascular necrosis and osteonecrosis

15.1.3 Injection Site Reaction Symptoms

Injection site reactions (ISRs) associated with single symptoms are recorded on the AE page (as a single symptom). ISRs with multiple symptoms are recorded as an AE of "Injection Site Reaction" on the AE page and the associated individual symptoms are recorded on the ISR symptom page.

In order to describe all ISR symptoms recorded, summaries will be based on the data collected on the ISR Symptoms page and also those single symptoms recorded as an adverse event.

Incidence and exposure-adjusted event rates of ISR Symptoms will be summarized by PT and separately by cohort and overall by treatment group using format as specified in Table 5.4.

ISR Symptoms will be listed.

15.2 Clinical Laboratory Tests

Clinical laboratory tests (hematology, chemistry, and urinalysis) are performed at Screening, and pre-dose at Day 1, Day 8, Week 3, Week 6, Week 20, Week 39, Week 52 and early termination visit.

All summary tables will include laboratory assessments from baseline up to 30 days post treatment discontinuation. Results will be reported separately as hematology, chemistry, urinalysis, and "other laboratory tests".

Laboratory tests will be graded as low/normal/high based on laboratory normal ranges. In addition, for laboratory tests with CTC grading available, all non-missing numeric results will be used to determine CTC grade programmatically, based on CTCAE v4.03.

For the following parameters, the distinction is made between significantly low/high results:

- Glucose (Hypoglycemia/Hyperglycemia)
- Hemaglobin (Anemia/Hemaglobin increased)
- Lymphocytes (Lymphocyte count decreased/Lymphocyte count increased)
- Potassium (Hypokalemia/Hyperkalemia)
- Sodium (Hyponatremia/Hypernatremia)
- Calcium (Hypocalcemia/Hypercalcemia)

The absolute values for pre-dose laboratory results at each scheduled visit, change from baseline in pre-dose laboratory results, and percent change from baseline in pre-dose laboratory results at each scheduled visit will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

Shift tables from baseline to worst post-baseline value (including scheduled and unscheduled visits) based on the CTC grading (Normal – Grade 5) will be generated for each Lab parameter where CTCAE grading is available, excluding parameters where CTCAE Grade does not rely on quantitative results alone (e.g. potassium and uric acid). Percentages are based on the number of subjects with each Baseline CTCAE grade (Normal, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, Missing, Overall). Shift tables will be produced separately by cohort and overall by treatment group using format as specified in Table 5.4.

For laboratory tests where grades are not defined by CTCAE, or where CTCAE grading does not rely on quantitative results alone (e.g. potassium and uric acid), shift tables will be generated using the low/normal/high classification to compare to baseline to the worst post-baseline value.

Line plots of the mean results (+/- SD) for the pre-dose windowed absolute values including all scheduled visits will be provided for the following parameters by treatment group by cohort. Data from the sentinel subjects and randomized subjects received active treatment within each cohort will be pooled:

- Hematology: erythrocytes, hematocrit, hemoglobin, leukocytes, neutrophils, platelets, WBC and RBC count.
- Chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin, blood urea nitrogen, calcium chloride, creatinine, direct bilirubin, glucose, lactate dehydrogenase, phosphate, potassium, protein, sodium, thyrotropin, vitamin D.

Listings:

In addition to the above tables, the following listings will be provided and will contain CTC grade and laboratory reference ranges:

- Hematology results
- Chemistry results
- Urinalysis results
- Urine chemistry results
- Other laboratory test results

- Laboratory results with CTCAE Grade ≥ 3

Listings will include all reported data and will be ordered by cohort, sentinel/randomized subject, subject ID, and assessment date.

15.3 Vital Signs

Vital Signs (heart rate, systolic/diastolic blood pressure, respiratory rate, and body temperature) are assessed at Screening, Day 1, Day 2, Day 3, Day 8, Week 3, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, safety follow-up visit, and early termination visit.

All summary tables will include vital signs recorded from baseline up to 30 days post treatment discontinuation.

The vital signs that are collected pre-dose and post-dose. Vital sign assessment frequency is shown below.

Table 15.3.1: Vital Sign Post-dose Assessment Frequency

Vital Sign Assessment Frequency				
Screening	After at least 5 min of rest, subject's vital signs are taken, preferably in sitting or supine position. Vital sign measurements should be repeated and documented 3 times with at least 5 min intervals between assessments.			
	Assessment Frequency			
Dosing Visits	**0-1 hr post-dose**	**0-2 hr post-dose**	**2-4 hr post-dose**	**4-8 hr post-dose**
Days 1, 2		q 15 min (± 5 min)	q 30 min (± 5 min)	q 60 min (± 10 min)
Days 3, 8		q 15 min (± 5 min)	q 30 min (± 5 min)	
Subsequent dosing visits	q 15 min (± 5 min); final assessment prior to end of visit (if longer than 1 hr)			

The absolute values for pre-dose vital signs at each scheduled visit, and change from baseline in pre-dose vital signs at each scheduled visit will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

Line plots will be generated, which present the mean pre-dose and post-dose absolute values (+/-SD) for each visit by treatment group by cohort. Data from the sentinel subjects and randomized subjects received active treatment within each cohort will be pooled.

The percentage of subjects experiencing at least one instance of a decrease of 20% in diastolic blood pressure from pre-dose to same-day post dose will be summarized by visit and for overall (each subject meeting criteria at any time in the study will be counted only once) for both sentinel subjects and randomized subjects.

Shift tables (Diastolic BP <40mmHg, Diastolic BP ≥40mmHg) from pre-dose to lowest same-day post-dose value category (Diastolic BP <40mmHg, Diastolic BP ≥40mmHg) will

be generated by visit and for overall (each subject meeting criteria at any time in the study will be counted only once) for both sentinel subjects and randomized subjects.

Shift tables (Diastolic BP <30mmHg, Diastolic BP ≥30mmHg) from pre-dose to same-day lowest post-dose value category (Diastolic BP <30mmHg, Diastolic BP ≥30mmHg) will be generated by visit and for overall (each subject meeting criteria at any time in the study will be counted only once) for both sentinel subjects and randomized subjects.

Shift tables (Systolic BP < (70mmHg plus 2 x Age), Systolic BP ≥ (70mmHg plus 2 x Age)) from pre-dose to lowest same-day post-dose value category ((Systolic BP < (70mmHg plus 2 x Age), Systolic BP ≥ (70mmHg plus 2 x Age)) will be generated by visit and for overall (each subject meeting criteria at any time in the study will be counted only once). Subject's age used in this calculation is the integer value.

A listing of vital sign data will also be provided.

15.4 Biological Parental Standing Height

If available standing height of the subject's biological parents will be listed.

15.5 Electrocardiogram

Electrocardiogram (ECG) data are recorded at Screening, Day 1, Day 8, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, safety follow-up visit, and early termination visit.

ECG assessments are performed in triplicate on Day 1 (pre-dose and post-dose) and on study day visits (post-dose only).

Summaries will be provided over all planned assessments, and repeated with the requirement that all post-dose ECG assessments should occur around the expected time of CMax, i.e., 20-40 minutes post-dose. The mean results of the ECG assessments meeting these criteria will be used for summaries and analyses.

All measures and means of the measures will be included in the listings.

The following ECG results will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4 at scheduled visits:

- ECG Mean Heart Rate (beats/min)
- QT interval (msec)
- QTcF interval (msec)
- PR interval (msec)

- RR interval (msec)
- QRS Duration (msec)

The following endpoints will be summarized at scheduled visits, and across all time points (using the highest mean QTc value), and presented by cohort and overall by treatment group using format as specified in Table 5.4.

- Percentage of subjects with QTcF >450 to ≤480ms, >480 to ≤500ms, >500 msec

The following endpoints will be summarized at scheduled visits, and across all time points, and presented by cohort and overall by treatment group using format as specified in Table 5.4

- Percentage of subjects experiencing at least one instance of a (decrease in mean heart rate from pre-dose baseline >25% and a mean heart rate <50 beats/min) post-dose.
- Percentage of subjects experiencing at least one instance of an (increase in mean heart rate from pre-dose baseline >25% and a mean heart rate >100 beats/min) post-dose.

The following endpoints will be summarized across all time points and presented by cohort and overall by treatment group using format as specified in Table 5.4.

- Percentage of subjects with a QTcF increase of 60ms from pre-dose baseline at any time
- Percentage of subjects with QTcF changes from pre-dose baseline of >30 and ≤ 60 msec, or >60 msec at any time

Listings will be provided and ordered by cohort, sentinel/randomized subject, treatment group, and visit:

- All ECG results.
- All ECG results for subjects with a QTc increase of 60msec from pre-dose baseline.

15.6 HPA Axis Assessments

To address potential effects of vosoritide on activation of the hypothalamic pituitary (HP) axis, assessment of salivary cortisol and serum prolactin levels will be analyzed at baseline, Week 26, Week 52 and early termination visit.

This data will be listed.

15.7 Child Behavior Checklist (Achenbach, 2000)

The Child Behavior Checklist (CBCL) 1.5- 5 years questionnaire is captured at Screening, Week 26, Week 52, and early termination visit.

All summaries will be generated on the Safety Population and include all assessments recorded up to 30 days following treatment discontinuation. Listings will include all reported data.

The CBCL 1.5-5 years old comprise questions addressing symptoms related to mood, behavior issues, and sleep disturbance. It is completed by the parent or primary caregiver.

The CBCL 1.5-5 years old consists of 100 questions, scored on a three-point Likert scale (0=Not True (as far as you know), 1= Somewhat or Sometimes True, 2=Very True or Often True). The time frame for item responses is the past 2 months.

Note: No data is collected from the language scale, as it is supplemental and not required to calculate any of the behavior measures.

The checklist yields scores in the following areas: emotionally reactive, anxious/depressed, withdrawn, somatic complaints, sleep problem, attention problems, and aggressive behavior.

The table in Appendix 25.2 shows how the domains are constructed with regards to the individual questions. The scores for each individual question within a domain are summed to give a domain score.

Each domain score above and total score will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4 at Baseline, Week 26 and Week 52 as well as change from baseline at Week 26 and Week 52 (where baseline measures exist).

Domain scores and total score will be listed by cohort, sentinel/randomized subjects, treatment group, and subject ID.

15.8 Echocardiogram

Echocardiogram results are only collected at the Screening visit, at safety follow up, and early termination visit if the previous assessment was done more than 3 months prior to early termination and will be listed by cohort, sentinel/randomized subjects, treatment group, and subject ID.

15.9 On-Study Procedures, Interventions and Surgeries

Any procedures, interventions of surgeries that occur on study (post first dose of study treatment) will be captured, along with start and stop date. These will be coded using MedDRA version 24.1 and will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4, and details provided in a listing.

15.10 Hip Monitoring and Rotation

All hip monitoring clinical assessments, including hip rotation, will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID, and assessment date.

15.11 Body Mass Index and BMI Z-scores

Weight (kg) and standing height are collected at Screening, Day 1, Day 2, Day 3, Day 8, Week 3, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, and early termination visit.

Standing height are recorded at Screening, Day 1, Week 6, Week 13, Week 26, Week 39, and Week 52.

Body Mass Index (BMI) will be calculated at each visit as:

$$\text{Body Mass Index (kg/m}^2) = \frac{Weight\ (kg)}{Height\ (m)2}$$

In calculation of BMI, in case standing height is not measured and body length is available, a derived standing height will be calculated; refer to Section **Error! Reference source not found.**.

Only for subjects aged 24 months or older, each measurement of BMI will be converted to an age-and sex-appropriate standard deviation score (SDS), also referred to as a Z-score, by comparison with reference data available for average stature children from the Centers for Disease Control and Prevention (CDC). The derived height mentioned above for BMI is also used for BMI in the calculation of BMI Z-score.

The absolute values at baseline, each 6-month visit, and change from baseline at each 6-month visits will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4 for both BMI and BMI Z-Score (again though, BMI Z-score will only be calculated for subjects aged 24 months or older).

All assessments will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID and visit.

15.12 Weight Z-Scores

Weight (kg) is measured at Screening, Day 1, Day 2, Day 3, Day 8, Week 3, Week 6, Week 13, Week 20, Week 26, Week 39, Week 52, and early termination visit.

Each measurement of weight will be converted to an age-and sex-appropriate SDS, also referred to as Z-score, by comparison with reference data available for average stature children from the CDC.

The weight of the subject on Day 1 will be used as the baseline measure, regardless of whether this is recorded pre or post-dose.

The absolute values and change from baseline at scheduled visits will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

All assessments will be listed for by cohort, sentinel/randomized subjects, treatment group, subject ID, and visit.

16 IMAGING SECONDARY ENDPOINT(S)

Imaging will be performed at screening, Week 52, and early termination visit:

Dual energy X-ray absorptiometry of whole body and spine

Anterior-posterior and lateral lumbar spine X-rays

Anterior-posterior X-rays of lower extremities

MRI data will be performed at screening, Week 52, and early termination visit to evaluate the effect of vosoritide on skull and brain morphology, including face, foramen magnum, ventricular, and brain parenchymal dimensions.

All summaries of imaging data and MRI data will be generated on the FAS and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

16.1 Lower Limb X-Rays

For each of the following parameters, the absolute values for both the left and right leg at Baseline and Week 52, and change from baseline at Week 52 will be summarized by cohort and overall by treatment group using the format as specified in Table 5.4:

- Left/Right Femur length (cm)
- Left/Right Fibula length (cm)
- Left/Right Tibia length (cm)
- Left/Right Tibia bowing angle (degrees)
- Left/Right Distance between ankle joint and distal growth plate of fibula (cm)
- Left/Right Lower Extremity (cm)
- Ratio of Left/Right Femur length (cm) to Tibia length (cm)
- Ratio of Left/Right Tibial length (cm) to Fibula length (cm)

In addition, change from baseline in tibial length (y-axis) at Week 52 will be presented on boxplots with a separate box for each leg and treatment group on the x-axis by cohort. Similar plots will also be generated for change from baseline in fibula length.

All assessments will be listed by cohort, treatment group, subject and visit.

16.2 Lumbar Spine X-Rays

Lumbar spine x-rays (AP and lateral views) assessments will be listed by cohort, treatment group, subject and visit.

16.2.1 Vertebral Height

Vertebral heights (anterior, medial, and posterior) will be measured for each individual vertebra (L1, L2, L3, L4, and L5).

The following ratios will be calculated for each individual vertebra (L1, L2, L3, L4, and L5) and reported to 1 decimal place:

- Anterior height (cm) to medial height (cm)
- Anterior height (cm) to posterior height (cm)
- Medial height (cm) to posterior height (cm)

For each of the vertebral height and the above ratios, the absolute values at Baseline and Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

16.2.2 Transverse Diameter (Interpedicle Distance)

The transverse diameter (interpedicle distance) will be measured for each individual vertebra (L1, L2, L3, L4, and L5).

For each transverse diameter vertebra, the absolute values at Baseline, Week 52, and the change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

In addition, change from baseline in transverse diameter (y-axis) for each individual vertebra (x-axis) will be presented on a boxplot at Week 52 for each cohort and treatment group.

16.2.3 Sagittal Width

The spinal canal width (sagittal width) will be measured for each individual vertebra (L1, L2, L3, L4, and L5).

For each individual vertebra, the absolute values at Baseline, Week 52, and the change from baseline Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

In addition, change from baseline in sagittal width (y-axis) for each individual vertebra (x-axis) will be presented on a boxplot at Week 52 for each cohort and treatment group.

16.2.4 Lumbar Spine Angles

The following angles will be measures on the lumbar spine x-rays:

- Sacral tilt (degrees)

- Lordosis (inward curve of the spine) (degrees)
- Kyphosis (convex curvature of the spine) (degrees)

Each angle will be measured on the spine x-rays and compared to Baseline at Week 52 to determine any worsening of sacral tilt, lordosis (inward curve of the spine) or kyphosis (convex curvature of the spine).

The absolute values of the sacral tilt, lordosis and kyphosis angles at Baseline, Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4.

A worsening in sacral tilt angle compared to baseline will be summarized [n(%)] by cohort by treatment group and overall at Week 52 as follows:

- Percentage of subjects with an increase in sacral tilt angle of ≥5 to < 10 degrees
- Percentage of subjects with an increase in sacral tilt angle of ≥ 10 degrees

A worsening in lumbar lordosis compared to baseline will be summarized [n(%)] by cohort by treatment group and overall at Week 52 as follows:

- Percentage of subjects with an increase in lordosis angle of ≥5 to < 10 degrees
- Percentage of subjects with an increase in lordosis angle of ≥ 10 degrees

A worsening in kyphosis angle compared to baseline will be summarized [n(%)] by cohort by treatment group and overall at Week 52 as follows:

- Percentage of subjects with an increase in kyphosis angle of ≥5 to < 10 degrees
- Percentage of subjects with an increase in kyphosis angle of ≥ 10 degrees

A listing of subjects experiencing a worsening in sacral tilt, kyphosis or lordosis will be provided.

16.3 Dual Energy X-ray Absorptiometry

A dual energy x-ray absorptiometry (DXA) scan is performed at Baseline and Week 52, in order to collect relevant BMC/BMD data (including Z-scores) for whole body less head, and the lumbar spine.

All DXA data will be summarized separately by cohort and overall by treatment group using the format as specified Table 5.4 for each scanner manufacturer (GE - Lunar Prodigy or Hologic – Discovery Horizon). Changes over time can only be interpreted if subjects use the same scanner consistently throughout the study. Subjects will be summarized according to the scanner used for their Baseline assessment. Subjects who have results from more than

one scanner type will be excluded from summaries, and their data will be listed only. All data will be listed.

16.3.1 Whole Body Less Head and Lumbar Spine

The absolute values at Baseline and Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4 for the following measures of bone mineral content (BMC) and bone mineral density (BMD):

- Whole Body Less Head BMC (g)
- Whole Body Less Head BMD (g/cm^2)
- Whole Body BMC (g)
- Whole Body BMD (g/cm^2)
- Lumbar Spine BMC (g)
- Lumbar Spine BMD (g/cm^2)

BMD Z-scores will be provided in the DXA reports, and the absolute values at Baseline and Week 52, and change from baseline at Week 52 will be summarized and presented by cohort and overall by treatment group using the format as specified in Table 5.4 by scanner for each of the following:

- Whole Body Less Head BMD Z-Score
- Whole Body BMD Z-Score
- Lumbar Spine BMD Z-Score

The absolute values of total body percent fat, android percent fat, and gyenoid percent fat will be listed.

Box plots of whole body less head BMD Z-Scores will be provided by cohort by treatment group and scanner.

16.4 MRI

For each of the following parameters and ratios, the absolute values, change from baseline and percent change from baseline at Week 52 will be summarized by cohort and overall by treatment group using the format as specified in Table 5.4:

Volume of Face

Volume of Sinus

Volume of Calvarium

Area of Foramen Magnum

Area of Spinal Cord at the FM Level

Whole Brain Total Volume

Ventricles Total Volume

Ratio of Face volume to Calvarium

Ratio of Area of Spinal Cord to Foramen Magnum

Ratio of Face volume to Sinus

MRI assessments for above variables, evidence of cervicomedullary, and spinal cord compression will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID and visit.

17 BONE METABOLISM BIOMARKERS

Bone metabolism biomarkers (both blood and urine) will be collected to assess changes in bone metabolism. The safety population will be used for all summaries.

Serum samples for bone metabolism blood biomarkers (collagen X and bone-specific alkaline phosphatase [BSAP]) are collected pre-dose at baseline, Day 8, Week 6, Week 20, Week 39, early termination visit. Urine samples for bone metabolism urine biomarkers (Cross-linked C-Telopeptide of Collagen Type II [CTX-II]) are collected pre-dose on Day 1, Day 2, Day 3, Week 3, Week 13, Week 26, Week 39, Week 52, and early termination visit.

For BSAP and Collagen X, the absolute values, and change from baseline at scheduled visits will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4.

For CTX-II, the absolute values normalized by creatinine, and change from baseline at scheduled visits will be summarized separately by cohort and overall by treatment group using format as specified in Table 5.4.

A box plot of change from baseline in BSAP, Collagen X, CTX-II normalized by urine creatinine over time will be provided for pooled sentinel subjects and randomized subjects received active treatment.

Bone metabolism biomarkers will be listed by cohort, sentinel/randomized subjects, treatment group, subject ID, and visit.

18 VOSORITIDE PD ACTIVITY BIOMARKERS

Samples for vosoritide activity urine biomarkers (cyclic guanosine monophosphate [cGMP] and urine chemistry (urine creatinine test) are collected pre-dose and post-dose (approximately 2-4 hours after study treatment administration) when possible, on Day 1, Day 2, Day 3, Week 3, Week 26, Week 39, Week 52, and early termination visit. Each urine collection will be tested for biomarker concentration and urine creatinine concentration for normalization.

The absolute values for pre-dose and post-dose urine cGMP normalized by creatinine at each scheduled visit and change from pre-dose to post-dose time points at each scheduled visit will be summarized and presented by cohort and overall by treatment group using format as specified in Table 5.4.

When possible, plasma PK samples with sufficient residual volume after completion of PK analysis will be used to measure changes in plasma cGMP after dose administration. Plasma samples will be collected for PK analysis on Day 1, Week 13, Week 26, Week 39, and Week 52. Plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose on scheduled visits. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes.

The absolute values for pre-dose and post-dose plasma cGMP at each scheduled visit and change from pre-dose to post-dose time points at each scheduled visit will be summarized and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

A box plot for the maximum change from pre-dose of plasma cGMP and change from pre-dose of urine cGMP normalized by creatinine by cohort by treatment group by visit will be provided.

Vosoritide activity urine biomarkers will be listed by cohort, sentinel/randomized subjects, treatment group and subject ID.

19 IMMUNOGENICITY ASSESSMENT

Serum samples for anti-drug antibody (ADA) testing will be drawn pre-dose on Day 1, Week 3, Week 13, Week 26, Week 52, and early termination visit. Blood (serum) samples for testing drug-specific IgE will be drawn on Day 1 and in the event of a Grade 3 or significant hypersensitivity adverse event, or at the investigator's discretion.

ADA testing will include anti-vosoritide total antibody (TAb); TAb cross-reactive with endogenous C-type natriuretic peptide (CNP), brain natriuretic peptide (BNP) or atrial natriuretic peptide (ANP); and anti-vosoritide neutralizing antibody (NAb).

NAb testing and TAb testing for cross-reactivity with endogenous CNP, ANP or BNP will be performed only on baseline and TAb positive samples. NAb testing will not be performed if the corresponding TAb is negative. A listing for each ADA assay will be provided.

Summary tables will include all safety events up to 30 days following treatment discontinuation. Listings will include all reported data.

The immunogenicity population will be used for all summaries. The data conversion rules for immunogenicity analysis are listed below:

Operational Data Conversion Table for Immunogenicity Analysis

Assay	Result Type	Result = "Concentration (Titer Units)"	Pos/Neg for Incidence Table	Numerical Value for Display	Numerical Value for Calculation
Anti-BMN111 TAb	Numeric Titer	Negative Screen	Negative	1	0
		Negative Immunodepletion	Negative	1	0
		Negative Titer (≤10)	**Negative**	**1**	**0**
		* Value * (e.g. 20, 30, …)	**Positive**	**e.g. 20, 30, …**	**e.g. 20, 30, …**
		Imputed values - none			
		MRD of assay: 10			
Anti-BMN111 NAb	Numeric Titer	Negative Screen	Negative	1	0
		Negative Immunodepletion	Negative	1	0
		Negative Titer (≤5)	**Negative**	**1**	**0**
		* Value * (e.g. 10, 20, …)	**Positive**	**e.g. 10, 20, …**	**e.g. 10, 20, …**
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			
		MRD of Assay: 5			
ANP Reactivity	Binary	Negative Screen	Negative		
		Negative Immunodepletion	Negative		
		Positive Immunodepletion	**Positive**		
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			
BNP Reactivity	Binary	Negative Screen	Negative		
		Negative Immunodepletion	Negative		
		Positive Immunodepletion	**Positive**		
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			
CNP-22 Reactivity	Binary	Negative Screen	Negative		
		Negative Immunodepletion	Negative		
		Positive Immunodepletion	**Positive**		
		Imputed values – if TAb negative then impute result as 'Negative' for same study visit			

The incidence [n(%)] of TAb titer positive results will be summarized for each scheduled visit, and overall (described as 'Ever Positive') as follows:

$$\frac{Number\ of\ subjects\ with\ a\ positive\ test\ result}{Number\ of\ subjects\ with\ non-missing\ TAb\ result} * 100$$

The incidence [n(%)] of NAb positive test results, and positive cross-reactivity results for ANP, BNP and CNP, will also be calculated based on the number of subjects with a non-missing TAb result, and summarized at each scheduled visit and overall.

The absolute values (numerical values) of TAb titers and NAb titers will be summarized at Day 1, Week 3, Week 13, Week 26, and Week 52, and presented separately by cohort and overall by treatment group using format as specified in Table 5.4.

The mean (SD) TAb titer, number of hypersensitivity adverse events (HAEs) excluding injection site reactions, and number of subjects experiencing HAE's will be summarized by the highest HAE CTCAE Grade, and presented by TAb status (negative or positive) and separately by cohort and overall by treatment group using format as specified in Table 5.4.

A line graph of the mean TAb titer (+/- SE) will be presented over time for each visit by pooled placebo, active for each cohort (pooled for sentinel and randomized subjects), and overall. A similar figure will be generated for NAb titers.

The relationship between immunogenicity (ADA status: negative or positive) and measures of safety and efficacy will further be presented graphically by treatment group:

- Box plot of change from baseline at week 52 in standing height/body length Z-Score by TAb status
- Box plot of change from baseline at week 52 in standing height/body length Z-Score by NAb status
- Box plot of change from baseline at week 52 in standing height/body length by by TAb status
- Box plot of change from baseline at week 52 in standing height/body length by NAb status
- Box plot of number of hypersensitivity adverse events by TAb status
- Box plot of number of hypersensitivity adverse events (excluding ISRs) by TAb status
- Box plot of number of injection site reaction adverse events by TAb status

- Box plot of maximum duration of injection site reaction adverse event by TAb status, where injection site hemorrhage, injection site hematoma, injection site bruising, and injection site induration will be excluded.

Should there be a significant relationship between TAb positivity and change from baseline at Week 52 in standing height/body length, a scatter plot of change from baseline in standing height/body length at Week 52 versus mean TAb titer in TAb positive subjects will be presented as a second tier analysis. The Pearson correlation coefficient will be included in the figure to describe the association.

In addition, the following listings will be provided:

- Total antibody titers and neutralizing antibody titers
- Hypersensitivity adverse events with antibody results
- Drug-specific IgE, total IgE, C4 and serum tryptase for hypersensitivity reaction visits
- Mean Tab and NAb titers, standing height/body length, standing height/body length Z-Scores, and AGV
- TAb cross reactivity to endogenous natriuretic peptides
- TAb cross reactivity by subject and cardiac disorder or HLGT ‘fluid and electrolyte imbalance’ related adverse event.

All immunogenicity listings will be ordered by cohort, sentinel/randomized subjects, treatment group, 4-digit subject ID (i.e., the subject ID excluding the site number), and visit.

20 PHARMACOKINETICS AND PHARMCODYNAMICS

Vosoritide concentrations and PK parameters will be summarized descriptively by visit for all subjects in the PK population. If supported by the data, impact of demographics and immunogenicity on PK parameters and the exposure-response relationship between vosoritide exposure and efficacy, biomarker, and safety pharmacodynamic (PD) endpoints of interest will be explored. Details on the PK and PK/PD analyses are separately documented in the Clinical Pharmacology Analysis Plan.

21 OTHER ANALYSES

To evaluate the impact of COVID-19 pandemic on the study conduct and results (assumed started from 1st January 2020 up until the date of data finalization), the following new outputs will be presented separately by cohort and overall by treatment group using format as specified in Table 5.4:

1. For all protocol scheduled visits, number of missed visits, late visits, and clinical site visits changed to virtual or home visits due to COVID-19 will be summarized.
2. COVID-19 has been added to the new MedDRA version 24.1. One AE listing will be produced that will include all AEs coded to Preferred Terms containing "COVID-19". Another AE listing will be produced that will be included all AEs occurring within 14 days following COVID vaccine.
3. A listing of concomitant medication of COVID vaccine will be provided.
4. COVID-19 specific protocol deviations will be listed and summarized.

22 ANALYSES DIFFERENT FROM PROTOCOL-DEFINED ANALYSES

Standing height/body length was one of the growth measurements included in the secondary efficacy endpoints in the protocol. It is the first key secondary efficacy endpoint in this SAP.

23 REFERENCES

Achenbach, T. M., & Rescorla, L. A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley–III) Technical Manual

Health Act CHQ: Infant and Toddler Quality of Life Questionnaire – 97 (itqol-97) © 2013

Hoover-Fong, JE, Schulze, KJ, Alade, AY, J, Bober, MB et. al. Growth in achondroplasia including stature, weight, weight-for-height and head circumference from CLARITY: achondroplasia natural history study – a multi-center retrospective cohort study of achondroplasia in the US. Orphanet Journal of Rare Diseases 16:522, 1-19. 2021.

https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

Uniform Data System for Medical Rehabilitation. 2016. *The WeeFIM II® Clinical Guide, Version 6.4*. Buffalo: UDSMR.

24 SUMMARY OF KEY CHANGES TO STUDY SAP

Version		Affected Section	Summary of Revisions
Number	Date		
1.1	17Nov2021	Section 14.1	Option OBSMARGINS was added in the PROC MIXED procedure.
		Section 15.1.2	Definition for Algorithmic Anaphylaxis SMQ has been updated.
		Section 19	"by cohort" was removed for box plots. Box plot for maximum severity of hypersensitivity adverse events by TAb status was removed. Injection site hemorrhage, injection site hematoma, injection site bruising, and injection site induration will be excluded for the box plot of maximum duration of injection site reaction adverse event by TAb status.
2.0	02Feb2022	Section 14.1	Per feedback from FDA, multiple imputation was added as imputation method if assessment at Week 52 is missing and there is no assessment after Week 52.
		Section 14.2.1	Per feedback from FDA, it was made clear that the primary analysis will be performed on randomized subjects only. "by _imputation_" was added in the PROC MIXED procedure to analyze the multiple imputed data, "PROC MIANALYZE" was added to summarize results from multiple imputation.
		Section 14.2.1 & Section 14.3	Age stratum was added as a covariate in the ANCOVA model since subjects were randomized by age stratum
		Section 14.2.1	Spaghetti plots for standing height/body length Z-Score were replaced by individual line plots and line plots of mean +/- SD.
		Section 14.3.1	Line plots of mean +/- SD for standing height/body length were added.
		Section 14.3.2	Individual line plots of cumulative AGV were added.
		Section 14.3.3	Individual line plots and line plots of mean +/- SD for upper to lower body segment ratio were added.

Version		Affected Section	Summary of Revisions
Number	Date		
		Section 14.4.6	Variables for sleep study scores were updated to be clear and consistent with the data collected.
		Section 15.3	By visit was added for the tables of change in blood pressures.
		Section 16.4	Percent change from baseline was added for summary of MRI.
		Section 23	Reference of achondroplasia data was updated.

25 APPENDICES

25.1 Summary of Growth Measures Derivations

Derived Value:	Measure required in calculation:	Age	Order of Substitution for measure required: 1 then 2.	
			1	2
BMI	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
AGV	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
Standing Height	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
Sitting Height	Height	Under 24 months	Crown-to-Rump Length	Sitting Height
		24 months or older	Sitting Height	Crown-to-Rump Length
Height Z-Score*	Height	Under 24 months	Body Length	Standing Height
		24 months or older	Standing Height	Body Length
BMI Z-Score**	BMI	Under 24 months	Will not be calculated	
		24 months or older	Standing Height	Body Length
Lower Body Length	Standing Height and Sitting Height	Under 24 months	Body Length - Crown-to-Rump Length	Standing Height - Sitting Height
		24 months or older	Standing Height - Sitting Height	Body Length - Crown-to-Rump Length
Arm Span to Height Ratio	Height	Under 24 months	Body Length	Standing Height

Derived Value:	Measure required in calculation:	Age	Order of Substitution for measure required: 1 then 2.	
			1	2
		24 months or older	Standing Height	Body Length
Upper to Lower Body Segment Ratio	Upper Body: Lower Body	Under 24 months	Crown-to-Rump Length: (Body Length - Crown-to-Rump Length)	Sitting Height: (Standing Height - Sitting Height)
		24 months or older	Sitting Height: (Standing Height - Sitting Height)	Crown-to-Rump Length: (Body Length - Crown-to-Rump Length)

*Height Z-Scores will be derived using CDC references and macro.

**BMI Z-Score will be calculated in the age appropriate CDC macros, only for subjects aged 24 months or older.

Programming will not supply the BMI value that we derive for our datasets and table summaries to this macro.

The CDC macro will calculate BMI Z-Scores using the Height value supplied as describe above to create the Height Z-Scores. Therefore, the BMI Z-Scores will be consistent with the Height Z-Score.

25.2 Child Behavior Checklist Domains

Domain/Subscale	CBCL 1.5-5
EMOTIONALLY REACTIVE	21. Disturbed by change 46. Twitches 51. Panics 79. Shifts between sad-excite 82. Sudden mood change 83. Sulks a lot 92. Upset by new 97. Whining 99. Worries
ANXIOUS/DEPRESSED	10. Too dependent 33. Feelings easily hurt 37. Upset when separated 43. Looks unhappy 47. Nervous 68. Self-conscious 87. Fearful 90. Unhappy, sad, depressed
WITHDRAWN	2. Acts too young 4. Avoids eye contact 23. Doesn't answer 62. Refuses active games 67. Unresponsive to affection 70. Little affection 71. Little interest 98. Withdrawn
SOMATIC COMPLAINTS	1. Aches, pains 7. Can't stand things out of place 12. Constipated 19. Diarrhea 24. Doesn't eat well 39. Headaches 45. Nausea 52. Painful bowel movements 78. Stomachaches 86. Too concerned with neatness 93. Vomits
SLEEP PROBLEMs	22. Doesn't want to sleep alone 38. Trouble sleeping 48. Nightmares 64. Resists bed 74. Sleeps little 84. Talks, cries in sleep 94. Wakes often

Domain/Subscale	CBCL 1.5-5
ATTENTION PROBLEMS	5. Can't concentrate 6. Can't sit still 56. Clumsy 59. Quickly shifts 95. Wanders away
AGGRESSIVE BEHAVIOR	8. Can't stand waiting 15. Defiant 16. Demands must be met 18. Destroys others things 20. Disobedient 27. Lacks guilt 29. Easily frustrated 35. Gets in fights 40. Hits others 42. Hurts unintentionally 44. Angry moods 53. Attacks people 58. Punishment doesn't change behavior 66. Screams 69. Selfish 81. Stubborn 85. Temper 88. Uncooperative 96. Wants attention

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