Official Title: A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia

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16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

Statistical Analysis Plan (SAP) (11JUN2018)

Statistical Analysis Plan Signature Pages

111-202 Clinical Pharmacology Analysis Plan (CPAP) (08JUN2018)

16.1.9.2 Data Monitoring Committee (DMC) Materials

DMC Charter

BMN 111-202 DMC Charter V1 (25OCT2013)

BMN 111-202 DMC Charter V2 (05SEP2014)

BMN 111-202 DMC Charter V3 (15MAY2015)

BMN 111-202_205 DMC Charter V4 (01FEB2016)

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Statistical Analysis Plan

Phase 2 Clinical Study Report

Study 111-202

A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia

Final

June 11th, 2018

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACH	Achondroplasia
ADA	Anti-drug antibody
AE	Adverse event
ANP	Atrial natriuretic peptide
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BMN	BioMarin
BSAP	Bone-specific alkaline phosphatase
BNP	Brain natriuretic peptide
cGMP	Cyclic guanosine monophosphate
CNP	C-type natriuretic peptide
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events (v4.0)
DMC	Data monitoring committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
ISR	Injection site reaction
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SC	subcutaneous

SMQ	Standardized MedDRA Queries
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

2 INTRODUCTION

Study 111-202 (protocol dated on 25 October 2013) is a phase 2, open-label, sequential cohort dose-escalation study designed as a proof of concept study for BMN 111 in children with Achondroplasia (ACH). This 6-month study will allow for assessment of the effect of daily BMN 111 administration on safety, tolerability, growth velocity, absolute growth, and body proportions. A clinically relevant increase in annualized growth velocity is considered to be in the range of 25%-50% change from baseline, although the targeted increase may be refined based on ongoing comprehensive safety and efficacy review of BMN 111. Additional exploratory endpoints that reflect the medical complications of ACH will also be evaluated.

Amendment 1 (dated on 03 June 2014) of this study establishes an optional, open-label extension period of approximately 18 months to commence at the end of the initial phase of the study, making a total study duration of approximately 25 months, including a 1-month safety follow-up visit. The rationale for extending this Phase 2 study is to assess the long-term safety and tolerability of BMN 111 in children with ACH; and to assess longer-term effects of BMN 111 on growth in these children.

Amendment 2 (dated on 08 May 2015) establishes higher doses in two additional cohorts. Cohort 4 and 5 doses of 30 µg/kg and up to 60 µg/kg respectively were selected with the intent to achieve exposures expected to result in further increases in growth velocity in children with ACH with an acceptable safety profile.

Amendment 3 (dated 26 Oct 2015) added thyroid function test to Month 24 of the open-label extension phase of the study to assess any changes in thyroid function over the course of the open-label extension phase.

Amendment 4 (dated 22 Aug 2016) removed Cohort 5 based on preliminary data from Cohort 4.

The purpose of this Statistical Analysis Plan (SAP) is to provide a comprehensive description of methods of the data analyses included in the Phase 2 clinical study report.

2.1 Objectives of Study

The primary objective of the initial 6-month period is:

- To evaluate the safety and tolerability of daily SC injections of BMN 111 administered for 6 months

The primary objective of the study extension is:

- To evaluate the safety and tolerability of daily SC injections of BMN 111 administered for up to 24 months

The secondary objectives of the study are:

- To evaluate change from baseline in annualized growth velocity following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate changes from baseline in growth parameters following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate changes from baseline in body proportions (upper arm to forearm length, upper leg to lower leg length, and upper to lower body segment ratios) following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate dose-exposure and PK profiles of BMN 111 in children with ACH following daily SC injections of BMN 111 at each dose level and over multiple days

The exploratory objectives of the study are:

- To evaluate change from baseline in QCT bone mineral density (BMD) following daily SC injections of BMN 111 administered for 6 months, and up to 24 months

- To evaluate changes from baseline in growth plate morphology following daily SC injections of BMN 111 for 6 months, and up to 24 months
- To evaluate changes from baseline in long-bone growth, and morphology of the spine following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate changes from baseline in sleep apnea following daily SC injections administered for 6 months, and up to 24 months
- To evaluate changes from baseline in elbow joint range of motion by goniometry, following daily SC injections administered for 6 months, and up to 24 months
- To evaluate changes from baseline in BMN 111 activity biomarkers and bone/collagen biomarkers following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate immunogenicity from baseline and assess impact on safety, PK, and efficacy measures following daily SC injections of BMN 111 during the 6 months, and up to 24 months

2.2 Study Design

The primary objective of this study is to assess the safety and tolerability of daily BMN 111 administered to children with ACH. Dose regimens will be assessed with four dosing cohorts. The study design is presented in Figure 2.2.1. Approximately 36 subjects who are 5 to 14 years old (inclusive) will be enrolled. A maximum of five children from one gender may be enrolled in each cohort if the total size of the cohort is eight or nine subjects; a maximum of six children from one gender can be enrolled in each cohort if the size of the cohort is 10 subjects.

Comprehensive outpatient safety monitoring will be conducted for all subjects after the first dose of study drug is received over the course of the first 10 days, followed by close monitoring throughout the duration of the study. The comprehensive safety monitoring includes a minimum of 8 hours post dose observation on the first two days of dosing and at least 4 hours post dose observation on study days 3 and 4. Subjects may be observed for a longer duration and/or additional visits may be added for further safety assessment on Days 5-9 at the discretion of the Investigator in consultation with the BioMarin Medical Monitor. A visit on Day 10 concludes the comprehensive outpatient safety-monitoring period. Vital signs will be monitored frequently during the initial period of Days 1-10, including approximately every 10-20 minutes for the first 2 hours post dose on visit days.

Additional safety assessments during this period are electrocardiogram (ECG), physical exams, AE assessment, and clinical labs.

BMN 111 will be administered as a morning dose in one of the following daily dosing regimens:

- Cohort 1: the first eight subjects will receive 2.5 µg/kg BMN 111.
- Cohort 2: the second eight subjects will receive up to 7.5 µg/kg BMN 111.
- Cohort 3: the third eight to ten subjects will receive up to 15.0 µg/kg BMN 111.
- Cohort 4: the fourth eight to ten subjects will receive 30.0 µg/kg BMN 111.

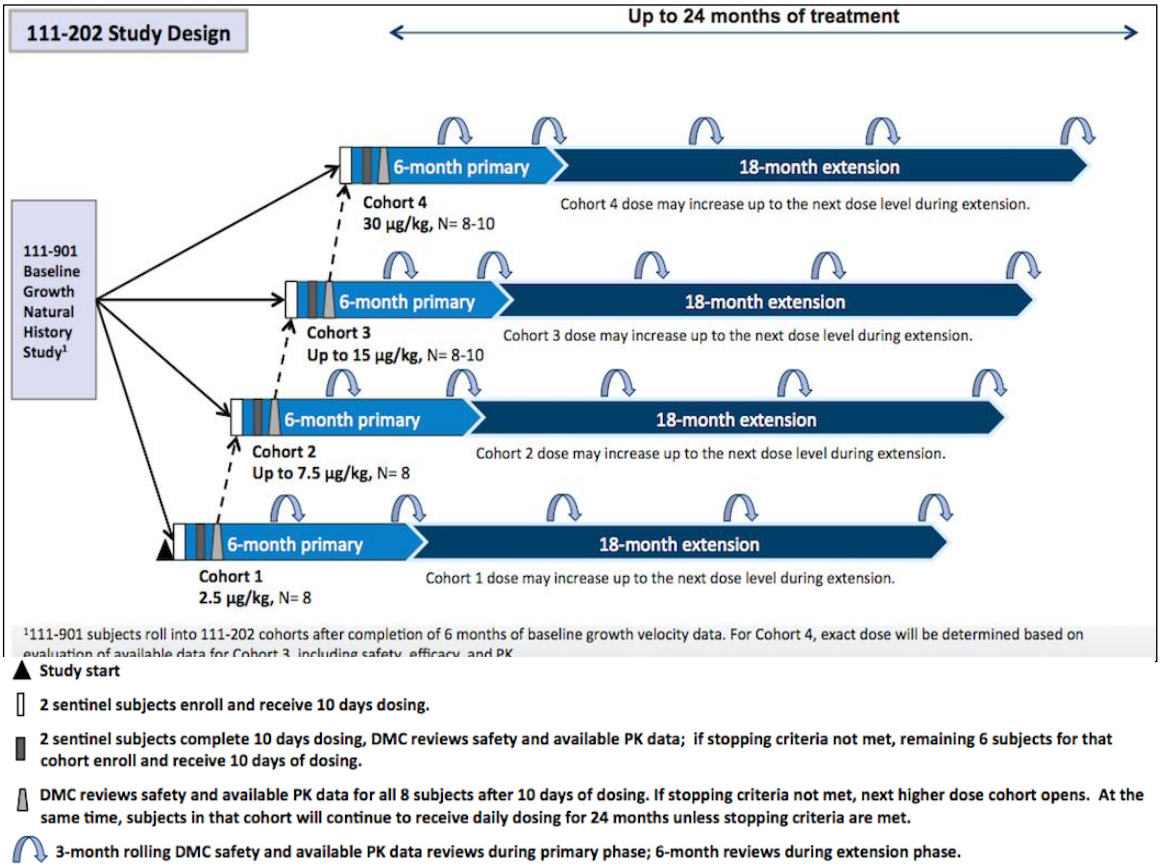
For each cohort, two sentinel subjects will be enrolled and monitored. A DMC review will occur after both sentinel subjects reach Day 10; if stopping criteria are not met, and after review and approval by the DMC, the remainder of the cohort may then be enrolled.

Subjects will remain on a daily fixed dose throughout the initial 6-month treatment period. Subjects in each cohort continue to receive daily dosing (Cohort 1, 2.5 µg/kg; Cohort 2, up to 7.5 µg/kg, Cohort 3, up to 15 µg/kg, and Cohort 4, 30 µg/kg) for 6 months unless stopping criteria are met. When clinical safety is established and stopping criteria are not met after all 8-10 subjects have completed at minimum their first

10 days of cohort dosing, and after DMC review and approval, the subsequent cohort may be open to enrollment.

In the 18-month optional, open-label extension period, eligible Cohorts 1 and 2 subjects were dose escalated to the 15µg/kg dose while Cohort 3 and Cohort 4 subjects continued at their respective starting doses of 15µg/kg and 30µg/kg, respectively, based on the pre-specified dose adjustment criteria described in the protocol and amendments.

Figure 2.2.1: Study Design



2.3 Study Population

Children 5-14 years old with ACH were chosen because subjects with ACH have an *FGFR-3* gain of function mutation and because preliminary efficacy evaluation, determined by change in annualized growth velocity, requires treatment of subjects prior to epiphyseal growth plate closure, which occurs in late adolescence. Growth velocity in children with ACH remains relatively stable from approximately 3 years old to growth plate closure (Hoover-Fong, 2008, Am.JClinNutr.). Children younger than 5 years old will not be enrolled in order to establish a safety profile in an older population first, as well as to minimize the confounding effects of nonlinear growth rates and inaccuracies inherent in measurement of recumbent length in young children.

2.4 Sample Size Determination

Approximately 8-10 subjects will be enrolled in each cohort to evaluate the safety and tolerability of BMN 111 in this population. No formal sample size calculations were performed.

2.5 Blinding and Randomization Methods

2.5.1 Blinding Method

No blinding or randomization was performed in this study.

2.5.2 Interim Analysis

No formal interim analyses for efficacy are planned for this study. However, efficacy data from the first three cohorts will be evaluated to inform decision-making regarding higher doses and summarized in the end of phase 2 report. Efficacy data will also inform the decision to increase a cohort dose if the initial dose exhibits suboptimal efficacy.

To address objectives of the study, analyses will be performed when all subjects have completed the initial 6-month period and when all available subjects have completed the extension period.

Additional exploratory analyses may be performed in the extension period.

3 GENERAL ANALYSIS CONSIDERATION

3.1 Analysis Populations

The following populations are defined for the initial 6-month period and the extension period, respectively. The number of subjects in each population will be summarized by cohort in the initial 6-month period and by dose level in the extension period.

3.1.1 Enrolled Population

All subjects who consented and were screened and eligible will be included in Enrolled population.

3.1.2 Efficacy Analysis Population

For each of initial 6-month period and the extension period, all subjects who receive at least one dose of study treatment and who have post treatment data for any efficacy endpoint in the corresponding period will be included in the Efficacy Analysis and Extension Efficacy Analysis population, respectively.

3.1.3 Safety Analysis Population

Safety Analysis Population consists of all subjects who receive at least one dose of study treatment and will be used for safety analysis in the initial 6-month period and entire study period**.**

Extension Safety Analysis Population consists of all subjects who receive at least one dose of study treatment in the extension period and will be used for safety analysis in the extension period.

3.2 Data and Cohort Presentation

All available data for study BMN111-202 will be used for the final analysis. Efficacy data collected in study BMN111-901 that is 12 months prior to screening in BMN111-202 for subjects who subsequently enrolled in study BMN11-202, and are included in the corresponding analysis population, will be summarized in efficacy tables and figures.

For the initial 6-month period, unless otherwise specified, all data will be presented for each cohort and all cohorts combined.

In the extension period, efficacy and imaging assessment data will be summarized for Cohorts 1 and 2 subjects who switched to 15µg/kg by cohort, and Cohort 1 and 2 combined.

In the entire study period, efficacy and imaging assessment data will be summarized for Cohort 3 and Cohort 4 separately, and Cohort 3 and 4 combined.

In the extension period, all other data will be summarized by dose level and all cohorts combined. For the entire study period, unless otherwise specified, safety data are summarized by dose level, and by cohort, and all cohorts combined. Subjects in Cohorts 1 and 2 may be represented at multiple dose levels and are accounted once for each dose level they receive.

3.3 Study Day Derivation

A study day will be obtained by subtracting the initial study drug start date from a visit date plus 1, if the visit date occurs after the initial study drug start date. Otherwise, the study day will be the visit date minus

the initial study drug start date. Therefore, Study Day 1 will be the same date as the initial study drug start date.

3.4 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. The analysis windows are designated for each scheduled visit and centered on a target day. 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 CRF page will be used.

Data in BMN111-901 for subjects who enrolled in BMN111-202 study and are included in the corresponding analysis population will be used in efficacy summary tables and figures. The analysis visits and windows for assessments in BMN111-901 are defined below in Table 3.4.1. The analysis windows for assessments in BMN111-202 are defined below in Table 3.4.2 for the initial 6-month period and the extension period. Unless otherwise specified, all analysis are based on derived visits.

Table 3.4.1: Visit Time Windows for Observed Assessments in BMN111-901

Derived Visit	Target Day[a]	Window[a]	
-6M	-183	-228	-138
-12M	-364	-409	-319

[a]Target days and window are relative to the Screening date from the Anthropometric CRF form in BMN111-202

Table 3.4.2: Visit Time Windows for Observed Assessments in BMN111-202

Derived Visit	Target Day[a]	Window
Initial 6-Month Period		
Baseline		The last assessment on or prior to the first dose unless otherwise specified.
Day 1	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 4	Day 4	Day 4 – Day 7
Day 10	Day 10	Day 8 – Day 12
Day 15	Day 15	Day 13 – Day 18
Day 22	Day 22	Day 19 – Day 25
Day 29	Day 29	Day 26 – Day 36
Day 43	Day 43	Day 37 – Day 64
Day 85	Day 85	Day 65 – Day 106
Day 127	Day 127	Day 107 – Day 155
Day 183	Day 183	Day 156 – The last date of the Day 183 visit or Day 190 for subjects not entering the extension period
Extension Period (For subjects who enter extension)		
Month 8	Day 243	Day 183 Visit Date + 1 – Day 273
Month 10	Day 303	Day 274 – Day 333
Month 12	Day 364	Day 334 – Day 410
Month 15	Day 456	Day 411 – Day 501
Month 18	Day 547	Day 502 – Day 592
Month 21	Day 638	Day 593 – Day 684
Month 24	Day 730	Day 685 – the actual date of the nominal month 24 visit regardless of the analysis day

[a] Target days are relative to the first dosing day.

For two [redacted] subjects, [redacted] and [redacted], the Month 24 visit in study 111-202 occurred on [redacted]2016 and [redacted]2016 respectively, and subjects were unable to complete all assessments, so returned to complete the Month 24 visit assessments within the allowed protocol window for this visit, on [redacted]2016 and [redacted]2016 respectively. The data from both these two visits are considered in the Month 24 assessments.

3.5 Handling of Dropouts and Missing Data

Subjects who discontinued prematurely after Day 10 will not be replaced. Missing dates or partially missing dates will be imputed conservatively for concomitant medications and AEs to ensure that an AE is considered treatment emergent and has the longest possible duration. [redacted]

4 SUBJECT DISPOSITION

Subject disposition will be summarized separately for two periods; the initial 6 month period, and the entire study.

The number of subjects enrolled, the number of subjects treated, the number of subjects who completed/continuing/discontinued treatment, and the number of subjects who completed/continuing/discontinued from the period will be summarized by cohort and across all cohorts.

5 DISCONTINUATION AND COMPLETION

Of the number of subjects enrolled, for subjects who prematurely discontinued the study, the primary reason for study discontinuation will be summarized by cohort in the initial 6-month period, and by dose level in the extension period.

6 PROTOCOL EXEMPTIONS AND DEVIATIONS

Protocol deviations, as recorded in the eCRF, will be summarized by cohort and overall. Subjects with any deviation, any major deviation, and any minor deviation will be summarized, along with the type of deviation. Summaries will be based on the Safety Population.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic information will be summarized for all subjects in the safety population. The demographics including age at enrollment, age group, sex, race, ethnicity, and Tanner stage at baseline will be summarized using descriptive statistics.

Age groups are defined based on the age at screening as follows:

- ≥ 5 and < 8 years of age
- ≥ 8 and < 10 years of age
- ≥ 10 and ≤ 14 years of age

Baseline subject characteristics, including height, weight, and BMI, will be provided for efficacy analysis population in the growth measures tables.

Tanner stage will be recorded at each visit and the number and percent of subjects at each stage will be summarised by cohort and overall.

8 MEDICAL HISTORY

Subject's chronic diseases, disorders, allergies, and surgeries in the past will be collected as general medical history. Medial history will be coded in accordance with MedDRA 19.1. General medical history will be summarized by system organ class (SOC) and by preferred term (PT) for the safety population. [redacted]

9 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

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

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

Concomitant medications will be summarized for overall study period. In the event the start date of a medication 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 drug then the start date will be imputed as the first dose date.
- 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 drug then the start date will be imputed as the first dose date.

In the event the stop date of a medication 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, the imputed date will be replaced with the study completed or discontinued date.

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) dictionary (Version September 2015). Prior and concomitant medication use will be separately summarized by Anatomical Therapeutic Chemical (ATC) medication class (Level 4) and preferred name (i.e., generic medication name). If a medication doesn't have ATC level 4, they are grouped as ATC Level 4 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. [redacted]

10 COMPLIANCE

Treatment compliance will be calculated based on the drug exposure records captured in eCRF and summarized for the safety analysis population.

The total amount of study drug taken will be calculated from the data collected on the drug dispensation CRF during the study. The total planned study drug intake (planned dose) will be calculated as the doses planned in corresponding treatment duration.

Percentage compliance will be derived from the total amount of study drug intake divided by the planned study drug intake, and multiplied by 100%:

$$\text{Treatment Compliance} = 100 \times \frac{TotalDrugTaken}{Total\ Planned\ dose}$$

, where planned dose is the protocol-specified dose which changes when subjects change/switch dose, and total drug taken takes into account any units left in the syringe.

Treatment compliance will be calculated and summarized by cohort and overall in the initial 6-month period. In the extension period, it will be calculated for each dose level a patient has ever taken and summarized by dose level for all cohorts combined. In the entire study period, it will be summarized by dose level for all cohorts combined, and by cohort and overall.

11 EXTENT OF EXPOSURE TO STUDY DRUG

For each of the initial 6-month, the extension period, and entire study period, total duration of study drug exposure, mean daily dose received (µg/kg), number of subjects who missed at least one dose, and number of days subjects missed at least one dose (for subjects who missed at least one dose) will be presented using descriptive statistics such as n, mean, SD, median, minimum, and maximum.

The number and percentage of subjects who permanently discontinue study drug during the initial 6-month period, the extension period, and entire study period will be provided along with the reason for study drug discontinuation.

The summaries will be presented for each cohort and overall in the initial 6-month period by dose level in for the extension period, and by dose level, by cohort, and all cohorts combined. [redacted]

12 EFFICACY EVALUATIONS

Efficacy analysis will be carried out for the initial 6-month period and the entire study period. Figures are reported on the efficacy populations. Summary tables and figures include assessments at 12 months and 6 months prior to screening (-12M and -6M Visits in Study 111-901). [redacted]

Some growth parameters were only optional to collect. These parameters are not included in the figures due to the sparse data. They are indicated in the tables [redacted]

The mean (or the non-missing measurement in case one of the two measurements is missing) of the two measurements recorded on the anthropometric measurements in the eCRF at each scheduled visit based on analysis windows will be used for the outputs/figures [redacted]

All assessments collected during the study are included in the outputs even if they occur following treatment discontinuation

The baseline annualized growth velocity (AGV) is established in the natural history study of Study 111-901, based on the standing height measurements in the 6 months prior to the screening visit of Study 111-202. For all other efficacy endpoints, the Baseline is defined as the last non-missing assessment prior to the first dose of study drug. Unless otherwise specified, efficacy analyses will be performed using available data at derived visits.

In the initial 6-month period, efficacy data will be summarized (absolute measures and change from baseline) by cohort and overall. With the exception of AGV, summaries include measurements from all scheduled assessments. Separate tables with testing are provided just for Day 183 including baseline just for those with assessment at Day 183.

In the entire study period, efficacy data will be summarized for Cohort 3 and Cohort 4 by cohort and Cohort 3 and 4 combined. Summaries include assessments from 12 months prior to screening (-12M Visit in Study 111-901) to up to the Month 24 Visit in study 111-202.

For Cohort 1 and 2 subjects who were switched to 15µg/kg dose level, the endpoints will be summarized by descriptive statistics at -12M, -6M, Baseline, Day 183, the first visit a patient was switched to 15µg/kg as well as the first visit with at least 6 months, and 12 months on 15µg/kg per cohort, and Cohort 1 and 2 combined. Absolute measures and changes from baseline, or change from first visit a patient was switched to 15µg/kg (as applicable), are provided. It is important to note that since the time when the subjects switched doses differs the interpretation of the summaries of data for subjects who switch should be considered with caution.

For all parameters, figures by cohort summarizing the means and SDs are provided for the visits included in the summary tables.

Exploratory testing

P-values and 95% confidence intervals for the change between baseline and the post-treatment assessment (i.e. calculated as post-treatment-baseline) will be provided for the endpoints AGV, height Z-score and body proportions at the Month 6, Month 12, Month 18 and Month 24 visits. No testing is performed for the cohort 1 and 2 switcher assessments.

All p-values will be considered descriptive and no adjustment for multiplicity will be made.

The p-values are derived from the two-sided paired t-test on the following pair of hypotheses:

H0: Change from baseline = 0

H1: Change from baseline ≠ 0

12.1 Primary Efficacy Endpoint

No primary efficacy endpoint is planned for this study.

12.2 Secondary Efficacy Endpoints

12.2.1 Annualized Growth Velocity

Annualized growth velocity (AGV) is defined as follows:

$$\text{AGV (cm/yr.)} = \frac{\text{Height at the End of the Interval (cm)} - \text{Height at the Beginning of the Interval (cm)}}{\text{Interval Length in Days}} \times 365.25$$

Where the interval length in days is calculated as interval end date – interval start date.

The interval for the calculation of the baseline AGV starts on the day of the visit in Study 111-901 that is 6 months prior to the date of the screening visit in study 111-202 and ends on the date of the screening visit in Study 111-202. A sensitivity analysis is included that considers baseline AGV derived over the 12 months prior to screening.

The AGV based on the interval between baseline and the current visit will be summarized at each 6 months (absolute and change from baseline) using descriptive statistics (mean, SD, median, 25th and 75th percentiles, minimum, and maximum).

In addition, the AGV based on the 6-month intervals will be summarized whereby AGV at each post-baseline visit is derived over the previous 6 month interval.

E.g. AGV at (Day 183 to Month 12) = ((Height at Month 12 Visit – Height at Day 183 Visit)/ (Date of Month 12 Visit – Date at Day 183 Visit)) x 365.25.

For Cohort 1 and 2 switchers the assessments do not include AGV 1st visit on 15 µg/kg.

Figures by cohort, summarizing the means and SDs, are provided for the visits included in the tables.

In addition, figures include by cohort scatter plots at each 6 month visit by age, sex and Tanner stage at the visit (genital for males/breasts for females), dot plots for baseline versus post-baseline assessment and individual spaghetti plots.

Cohort 3 and 4 AGV plots over the entire study period, (AGV from baseline and 6-month intervals). For Cohort 1 and 2 switchers, the mean (+/- SD) AGV at baseline, the 1st visit with at least 6 months, and 12 months on 15µg/kg will be plotted by cohort.

12.2.2 Key Growth Measures

Key growth measures include:

- Standing Height (cm)
- Sitting Height (cm)
- Lower Body Length (cm) – calculated as [Standing Height – Sitting Height]
- Upper Arm Length (cm)
- Lower Arm (Forearm) Length (cm)
- Upper Leg Length (Thigh) (cm)
- Tibial Length (cm)
- Knee to Heel Length (cm)

Summary tables and figures are provided as described above in Section 12.

A further figure of individual subject data is included: Spaghetti Plot of Standing Height with Age-Specific Non-ACH and ACH References by Cohort and Sex (in initial 6 month period, and entire study period).

12.2.3 Height and Weight Z-Scores

Height and weight will be converted to age-and sex-appropriate standard score (SDS), also referred to as Z-score, by comparison with normal reference standards (non-ACH) from the Centers for Disease Control and Prevention (CDC) database.

Summary tables and figures are provided as described above in Section 12.

Further figures of individual subject data are also included:

- Height Z-Scores Using Non-ACH References over Age Prior to Treatment (BMN111-901) and in Entire Study Period – Cohort 3 and 4
- Change from Baseline in Height Z-Scores Using Non-ACH References over Age by Subject and Cohort – Cohort 3 and 4
- Change from Baseline in Height Z-Scores Using Non-ACH References over Age by Subject and Cohort – Cohort 1 and 2 switchers

12.2.4 Body Proportions

The following body proportion ratios are assessed (* optional):

- Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height)
- Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length
- Upper to Lower Leg ratio:
    - Upper Leg Length (Thigh) / Knee to Heel Length

    - Upper Leg Length (Thigh)/ Tibial Leg Length
- Arm Span* to Height ratio: Arm Span / Standing Height

Summary tables and figures are provided as described above in Section 12.

12.2.5 Other Growth Measures

Some other growth measures are also summarized (* are optional):

- Arm span (cm) *
- Weight (kg)
- BMI (kg/m^2)
- Head Circumference (cm)
- Head Length (cm) *
- Foot: Length and Width (cm)
- Waist Circumference (cm) *
- Hand: Palm Length, Middle Finger Length, and Palm Width (cm)
- Chest: Mid-expiration, Maximum Inspiration, and Maximum Expiration (cm) *

Summary tables and figures are provided as described above in Section 12.

In addition to the summaries and figures described above, the further figure is included:

- Spaghetti Plot of Weight with Age-Specific Non-ACH References by Cohort, Sex in initial 6 month period, and entire study period.

13 EXPLORATORY ANALYSIS

13.1 Biomarker Analysis

Biomarkers assessed are (C-terminal cross-linked telopeptide of type II collagen [CTX-II]), chondrocyte and osteoblast activity (bone-specific alkaline phosphatase [BSAP]), bone formation (pro-collagen Type 1 N-terminal propeptide [P1NP]), osteocalcin; and markers of BMN 111 activity (cyclic guanosine monophosphate [cGMP], N-terminal propeptide of C-type natriuretic peptide [NT-proCNP], and atrial natriuretic peptide [ANP]).

CTXII, BSAP, PINP and Osteoblast will be evaluated by value and change from baseline to each scheduled visit. and cGMP, NT-proCNP, and ANP are assessed at the pre-dose and post dose assessment.

Tables will be summarized on the safety population by cohort and all cohorts combined in the initial 6-month period by dose level in the extension period, and by dose level, by cohort, and all cohorts combined in the entire study period. Figures will be summarized by cohort in the initial 6-month period, by dose level in the extension period, and by dose, by cohort, and all cohorts combined in the entire study period.

For CTX-II, BSAP, P1NP, and osteocalcin, post-baseline assessments on the day of escalation will be summarized under the previous dose.

For cGMP, NT-proCNP, and ANP, post-baseline assessments on the day of escalation will be summarized under the new dose.

13.2 Sleep Apnea Analysis

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 at Screening and on Days 85 and 183 of the initial phase, and Months 12 and 24 of the optional, open-label extension phase. Assessment of sleep apnea will include, but may not be limited to, determining the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index, AHI). Other exploratory analysis of sleep apnea may be performed.

The full list of variables to be summarised will be described in more detail in a separate appendix.

13.3 Imaging Assessment Analysis

Exploratory imaging assessment data to be evaluated include measurements of lumbar spine, lower extremity, bone age, QCT and will be summarised for the absolute measures change from baseline and percent change from baseline using the efficacy population. Difference between estimated skeletal bone age and chronological age will be calculated and reported in a summary table. In the initial 6-month period, imaging assessment data will be summarized by cohort and overall. In the entire period, the data will be summarized by descriptive statistics at each available derived visit for Cohort 3 and 4 and Cohort 3 and 4 combined. For Cohorts 1 and 2 subjects who were switched to 15µg/kg dose level, the data will be summarized with descriptive statistics at the first visit a patient was switched to 15 µg/kg as well as the first visit with at least 6 months and 12 months on 15µg/kg by cohort and Cohort 1 and 2 combined.

Mean value of QCT, x-ray lumbar spine, lower extremity, bone age at each time point will be plotted by cohort for Cohort 3 and 4 in the entire study period. For Cohort 1 and 2 switchers, the mean value of the

same imaging assessment data at baseline, 1st visit with at least 6 months and 12 months on 15ug/kg will also be plotted by cohort.

13.4 Elbow Joint Range of Motion

The value and change from baseline in the elbow joint range of motion to each scheduled time point will be summarized using descriptive statistics (mean, SD, median, 25th/75th percentile, minimum, and maximum). Results will be summarized for the efficacy population by cohort and overall in the initial 6-month period by dose level in the extension period, and by dose level, by cohort, and all cohorts combined in the entire study period. The value of the elbow joint range of motion at each time point for each individual will be plotted by cohort for the entire study period.

14 SAFETY EVALUATIONS

Safety analysis will be carried out for the initial 6-month period, the extension period, and the entire study period, respectively. For each of the periods, all subjects who receive at least one dose of study treatment in the corresponding period and have any post-treatment safety information will be included in the safety analysis. Safety will be assessed by examining the incidence, severity grade, and relationship to study drug of all treatment-emergent adverse events (TEAEs) reported during the study period In addition, all other safety measures including clinical laboratory results, vital signs, electrocardiogram (ECG) and Echocardiogram (ECHO) values will be assessed. Unless otherwise specified, the baseline for safety endpoints is defined as the last non-missing assessment prior to the first dose. Numeric parameters will be summarized by descriptive statistics including n, mean, SD, median, minimum, and maximum. Adverse events will be summarized by number and percentage. Change from baseline will be calculated when both baseline and post-baseline results are non-missing numeric values.

For the initial 6-month period, unless otherwise specified, safety data will be presented for each cohort and all cohorts combined.

For the extension period, unless otherwise specified, safety data are summarized by dose level and all cohorts combined.

For the entire study period, unless otherwise specified, safety data are summarized by dose level and by cohort and all cohorts combined.

Subjects in Cohorts 1 and 2 may be represented at multiple dose levels and accounted once for each dose level they receive. Note the following rules are applied to associate the safety measure to a specific dose:

- AEs are associated to the dose taken on the start date of the AE.
- For mean summaries of safety parameters at visits over the course of the study the assessments on the day of escalation will be summarized under the previous dose.
- For mean summaries assessing pre and post dose measure on a specific day the assessments on the day of escalation will be summarized under the new dose.

For all summary tables for patients who discontinue treatment, all safety assessments within 30 days from the treatment discontinuation date will be included in summary tables.

[redacted]

14.1 Adverse Events

Adverse events will be coded in accordance with MedDRA version 19.1. A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of study drug administration during the AE reporting period. After informed consent is obtained and the first administration of study drug, all non-serious AEs and SAEs reporting period begins and continues until 4 weeks following either the last administration of study drug or the early termination visit, whichever is longer. If the onset date or end date of an adverse event is partial, the same imputation rules described in Section 9 will be applied.

AEs are summarized by incidence rates and for specific tables also by exposure adjusted incidence rates:

- Incidence rates calculated as number of subjects with the event divided by the number of subjects in the population being assessed
- Exposure-adjusted incidence rates (EAIR) are calculated by dividing the total number of events by the total treatment exposure in the period under assessment for the subjects in the population being assessed. The exposure time for each subject is derived as the time from the date of first dose, to the date of the last dose in the period under assessment.

14.1.1 All Adverse Events

The following summaries will be provided for each period:

- Overall Summary of AEs
- TEAEs by System Organ Class (SOC), Preferred Term (PT), and severity
- TEAEs assessed by investigators as related to study drug by SOC, PT and severity
- TEAEs by PT
- TEAEs by SOC
- Serious AEs (SAEs) by SOC and PT
- TEAEs leading to discontinuation by PT
- Incidence and exposure-adjusted event rates of TEAEs by SOC and PT

AEs of Special Interest

- Injection site reactions by SOC, PT, and severity
- Frequency and duration of ISRs
- ISR symptom by SOC, PT and severity
- Incidence and exposure-adjusted event rates of Hypotension TEAEs by SOC and PT
- Incidence and exposure-adjusted event rates of Heart Rate Change TEAEs by SOC and PT
- Incidence and exposure-adjusted event rates of events suggestive of Hypotension TEAEs by SOC and PT
- Incidence and exposure-adjusted event rates of Hypersensitivity TEAEs (SMQ) by SOC and PT
- Incidence and exposure-adjusted event rates of Hypersensitivity TEAEs (excluding ISRs) by SOC and PT
- Incidence and exposure-adjusted event rates of ISRs TEAEs by SOC and PT

Search criteria for the ADR/SMQ search criteria:

- Injection Site Reaction (ISR)
    - TEAEs are identified using having high level terms of MedDRA of 'Injection Site Reaction'
    - ISR Symptom page, which captures additional symptoms associated with a specific ISR AE
- Hypotension
    - TEAEs are identified as 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
    - TEAEs suggestive of Hypotension are identified as PT: Fatigue, Nausea, Loss of consciousness, Vision blurred, Cold sweat, Dizziness, Syncope, Presyncope.
- Heart Rate Change
    - TEAEs of Heart Rate Change are identified as PT: Atrial tachycardia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Sinus tachycardia, Supraventricular tachycardia, Tachycardia, Tachycardia paroxysmal, Ventricular tachycardia, Bradycardia.
- Hypersensitivity – refer to BioMarin pharmacovigilance standard search terms
    - TEAEs – Broad Hypersensitivity SMQ (421 narrow and broad search term PTs)
    - [redacted]

A figure is provided for Mean Frequency of Injection Site Reactions by Month in Entire Study Period for all Cohorts by Dose

[redacted]

[redacted]

14.2 Clinical Laboratory Tests

Summaries are provided for the 6 month period by cohort, the extension period by dose, and the entire study period by dose and by cohort. Descriptive statistics for clinical laboratory tests and change from baseline at each scheduled visit based on analysis windows will be presented.

Shift table from baseline to most extreme post-baseline value (including scheduled and unscheduled visits) based on the CTC grading (Grade 0 - 4 where available) will also be generated for each parameter as appropriate. Percentages are based on the number of subjects with each Baseline CTCAE grade.

All non-missing numeric results will be used to determine CTC grade based on CTCAE v4.0. Summary tables consider all lab assessments from baseline up to 30 days post treatment discontinuation. [redacted]

[redacted]

Lab parameters assessed

Hematology: (counts for differentials)

Blood Chemistry

Urine: Chemistry

Urinalysis

Other labs

For the initial 6-month period, clinical laboratory tests will be presented for each cohort and all cohorts combined. For the extension period, clinical laboratory tests are summarized by dose level. For the entire study period, clinical laboratory tests are summarized by dose level, by cohort, and all cohorts combined.

Figures are provided for each of the lab parameters summarized in the tables (1) by cohort for the first 6 months (2) by dose for the extension (3) for the entire study period by cohort.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

14.3 Vital Signs

Descriptive statistics for pre-dose vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperatures available) at each scheduled visit based on analysis windows will be presented.

Except for respiratory rate and temperature, change from pre-dose to multiple post-dose time points at specific time points will also be summarized.

For the initial 6-month period, mean vital signs will be summarized for each cohort and all cohorts combined.

For the extension period, vital signs are summarized by dose level and summaries.

For the entire study period, vital signs are summarized by dose level, by cohort, and all cohorts combined.

Figures will be summarized for each study period for pre and post dose assessments.

Dot Plot of Change from Pre-dose at Each Time Point for Systolic Blood Pressure/Heart Rate on Day 1 and Day 2 are also provided

[redacted]

14.4 Electrocardiogram and Echocardiogram

Descriptive statistics for pre-dose Electrocardiogram (ECG) results at each scheduled visit based on analysis windows will be presented. For the initial 6-month period, ECG data will be presented for each cohort and all cohorts combined. For the extension period, ECG data are summarized by dose level. For the entire study period, ECG data are summarized by dose level, by cohort, and all cohorts combined.

Both ECG and Echocardiogram (ECHO) results will be listed by subject.

14.5 Hip Monitoring

All hip monitoring assessments will be listed by subject.

14.6 Tanner Stage

All tanner stage assessments will be listed by subject.

14.7 Immunogenicity Analysis

Anti-drug antibody (ADA) tests will be performed using validated immunogenicity assays. Serum samples for ADA tests will be collected at each scheduled visit described in the protocol and amendments. ADA tests will include anti-BMN 111 total antibody (TAb); TAb cross-reactive with endogenous CNP, BNP or ANP; and anti-BMN 111 neutralizing antibody (NAb). NAb testing will not be performed if the TAb is negative. [redacted]. Immunogenicity will be summarized for the entire study period, by cohort, and all cohorts combined. Additionally, immunogenicity will be assessed for correlations with measures of safety and efficacy by analyzing ADA positive and negative subjects.

Specifically, change in growth velocity from baseline by ADA status (ADA negative and ADA positive) will be presented using box plots. Incidence of hypersensitivity adverse events (including/excluding ISRs) in ADA negative and positive subjects will be summarized using box plots.

The data conversion rules for immunogenicity analysis are listed in section 18.0.

14.8 Pregnancy Testing

Female subjects who have begun menses or are ≥ 10 years old will have a urine or serum pregnancy test at the time points specified in the Schedule of Events. Female subjects with a positive pregnancy test at Screening do not meet eligibility criteria for enrollment. Serum pregnancy tests will be performed in the event that urine pregnancy test results are positive or equivocal.

[redacted]

15 PHARMACOKINETICS ANALYSIS

The pharmacokinetics analysis plan will be documented in a separate document.

16 REFERENCES

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.

17 SUMMARY OF KEY CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
Draft SAP	July 2015	Efficacy	Inclusion of -12M and -6 M data from 901 study
Draft SAP	July 2015	Exploratory	Removal of the exploratory population definition
Draft SAP	July 2015	Safety	Addition of Tanner stage table
Draft SAP	July 2015	Safety	Update safety population definition
Draft SAP	July 2015	Safety	Creation of separate appendix for sleep apnea
Draft SAP	July 2015	Efficacy	Clarification on windowing for two [redacted] subjects [redacted] and [redacted].
Draft SAP	July 2015	Safety	Addition of protocol deviation table
Draft SAP	July 2015	Efficacy	Non confirmatory testing on the endpoints AGV, height Z score and the upper lower body ratios at D183 M12, M18 and M24
Draft SAP	July 2015	Efficacy	Use of ACH references for subject spaghetti plot references

18 APPENDIX

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			

BIOMARIN

SART Document Approval Form

Study name: BMN 111-202

Overview

Purpose (Check only 1):

- ☐ Final draft SAP
- ☐ Revision(s) to the final draft SAP
- ☑ Final SAP
- ☐ Amendment(s) to the final SAP
- ☐ The TOC of TLGs defined by the SAP
- ☐ TLG mockups and specifications defined by a SAP
- ☐ Revision(s) to the TLG mockups and specifications document after its approval, determined by the Biostatistican to require SART approval
- ☐ Request(s) for major changes to mockups and specifications after review of TLG outputs produced for the Dry Run
- ☐ Other:

Comments

Approval

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Signing Time: 6/14/2018 3:29:55 PM PDT

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Signing Time: 6/20/2018 7:08:09 PM PDT

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105 Digital Drive

Novato, CA 94949

Clinical Pharmacology Analysis Plan (CPAP)

A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia

Protocol Number: 111-202

June 8, 2018

APPROVALS

Lead Clinical Pharmacology Scientist:

[redacted] 8 JUNE 2018

Date

[redacted], Ph.D.

Scientist I, Clinical Pharmacology

BioMarin Pharmaceutical Inc.

Approver:

[redacted] 8 June 2018

Date

[redacted], Ph.D.

[redacted], Clinical Pharmacology

BioMarin Pharmaceutical Inc.

TABLE OF CONTENTS

1 INTRODUCTION

This clinical pharmacology analysis plan was developed after review of protocol 111-202. This plan describes the core set of planned analyses of the clinical pharmacokinetic (PK) and pharmacodynamic (PD) data from this study. Descriptions of the planned data preparation, analysis methods to be used and tables and figures to be presented in the clinical pharmacology report are provided in this document. The final methods of analysis implemented and results generated will be reported in the clinical pharmacology report and included as an appendix in the clinical study report. The bioanalytical method will be described in a separate report and referenced in the clinical pharmacology report. Any deviation from this plan will be documented in the appropriate section of the clinical pharmacology report.

2 STUDY OBJECTIVES

The primary objective of the initial 6-month period was to evaluate the safety and tolerability of daily subcutaneous (SC) injections of BMN 111 administered for 6 months.

The primary objective of the open-label extension phase was to evaluate the safety and tolerability of daily SC injections of BMN 111 administered for up to 24 months.

The secondary objectives of the study were:

- To evaluate change from baseline in annualized growth velocity following daily SC injections of BMN 111 administered for 6 months, and up to 24 months.
- To evaluate changes from baseline in growth parameters following daily SC injections of BMN 111 administered for 6 months, and up to 24 months.
- To evaluate changes from baseline in body proportions (upper arm to forearm length, upper leg to lower leg length, and upper to lower body segment ratios) following daily SC injections of BMN 111 administered for 6 months, and up to 24 months.
- To evaluate the exposure and PK profiles of BMN 111 in children with ACH following daily SC injections of BMN 111 at each dose level and over multiple days.

The exploratory objectives of the study were:

- To evaluate change from baseline in quantitative computed tomography (QCT) bone mineral density (BMD) following daily SC injections of BMN 111 administered for 6 months, and up to 24 months.
- To evaluate changes from baseline in growth plate morphology following daily SC injections of BMN 111 for 6 months, and up to 24 months.
- To evaluate changes from baseline in long-bone growth, and morphology of the spine following daily SC injections of BMN 111 administered for 6 months, and up to 24 months.
- To evaluate changes from baseline in sleep apnea following daily SC injections administered for 6 months, and up to 24 months.
- To evaluate changes from baseline in elbow joint range of motion by goniometry, following daily SC injections administered for 6 months, and up to 24 months.
- To evaluate changes from baseline in BMN 111 activity biomarkers and bone/collagen biomarkers following daily SC injections of BMN 111 administered for 6 months, and up to 24 months.
- To evaluate immunogenicity from baseline and assess impact on safety, PK, and efficacy measures following daily SC injections of BMN 111 during the 6 months, and up to 24 months.

3 STUDY DESIGN

Study 111-202 was a pediatric, Phase 2, open-label dose-escalation study to assess the safety and tolerability of daily BMN 111 administered to up to 35 subjects with a clinical diagnosis of ACH. Subjects who were 5 to 14 years old inclusive, with documented ACH confirmed by genetic testing, had at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry, and who met the study eligibility criteria were to be eligible to participate in this study. The Study 111-202 design is presented in Figure 3.1.

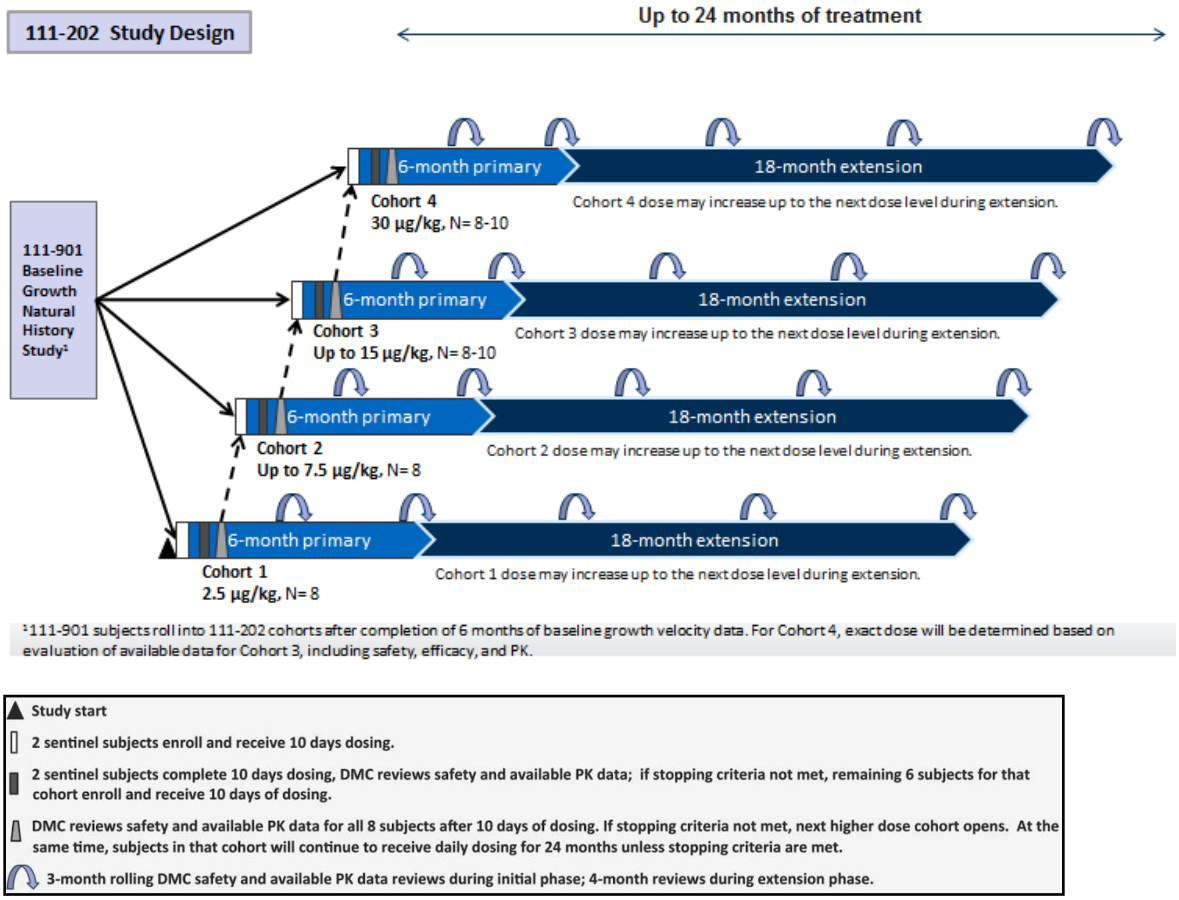
A maximum of 5 children from 1 gender were to be enrolled in each cohort if the total size of the cohort was 8 or 9 subjects; a maximum of 6 children from 1 gender could be enrolled in each cohort if the size of the cohort was 10 subjects.

Subjects remained on a fixed daily dose throughout the initial 6-month treatment period. Subjects in each cohort receive daily BMN 111 SC dosing (Cohort 1, N=8, 2.5 µg/kg; Cohort 2, N=8, up to 7.5 µg/kg, Cohort 3, N=8-10, up to 15 µg/kg, Cohort 4, N=8-10, 30.0 µg/kg) for 6 months unless stopping criteria were met. This was immediately followed by an optional, open-label extension period of approximately 18 months to commence at the end of the initial phase of the study, making a total study duration of approximately 25 months, including a 1-month safety follow-up visit. The rationale for extending this Phase 2 study was to assess the long-term safety and tolerability of BMN 111 in children with ACH; and to assess longer-term effects of BMN 111 on growth in these children.

In the 18-month optional, open-label extension period, subjects within each cohort either remained on the same dose that they received during the initial 6 months of treatment, or the dose for all subjects in the cohort was increased based on the following rules:

1. Initial dose was determined to exhibit suboptimal efficacy based on growth measurements after at least 6 months of treatment based on the review of the data for all subjects in the cohort.
2. Initial dose, and other doses higher than the initial dose, but lower than the dose to which the cohort was being increased were generally well tolerated for at least 6 months based on review of data for all subjects in the cohort.
3. The dose to which the subjects in the cohort were being escalated had been previously shown to be well tolerated for at least 10 days of comprehensive outpatient safety monitoring, based on a review of the data for all subjects in the cohort previously assigned to the considered dose.

Figure 3.1: BMN 111-202 Study Design



4 NUMBER OF SUBJECTS PLANNED

A total of up to 35 subjects were to be enrolled in the study (N=8 subjects for Cohort 1, N=8 subjects for Cohort 2, N=8-10 subjects for Cohort 3 and N=8-10 subjects for Cohort 4).

5 DATA HANDLING

5.1 Data Source and Archival

Plasma BMN 111 concentration-time data and the other required data such as demographics and dose records will be transferred from BioMarin's Biometrics Department in an appropriate SAS dataset format.

Source and analysis datasets will be stored in the appropriate Livelink folder in accordance with *SOP-104400 Preparing a Clinical Pharmacology Report*.

5.2 Missing Values

Missing concentration values will be ignored in graphic presentations, descriptive statistics, and the computation of PK parameters. No imputation of missing concentration values will occur.

Concentration records without the associated sampling or dosing time data will be also be ignored in graphic presentations, descriptive statistics, and the computation of PK parameters. Nominal time will not be imputed.

5.3 Measurements below the Lower Limit of Quantification

For PK analyses, concentration values below the lower limit of quantification (LLOQ) of the analytical method that are associated with time points prior to T_{max} will be replaced by zero. Concentration records below the LLOQ that are associated with time points occurring after T_{max} will be treated as missing. Concentration values below the LLOQ that are embedded between two quantifiable concentrations (quantifiable concentration immediately prior and immediately following) will be treated as missing.

5.4 Outlier Handling

On a case by case basis, it may be necessary to exclude anomalous or erroneous individual PK concentration values from the calculation of derived PK parameters. It is up to the scientific judgement of the clinical pharmacology (CP) scientist to exclude such cases. Reasons may include dose administration error or major protocol violations with an impact on PK. Exclusion of data along with reasons should be reported in the appropriate section of the CP report.

5.5 Representation of Mean Concentrations

The central tendency of PK profiles will be graphically depicted as mean concentration-time profiles constructed using nominal sampling times. Mean concentration values will be calculated and reported only if three non-missing values are present for the nominal time point. Concentration values below the LLOQ will be treated as zero in the mean concentration calculations. If the mean concentration value is less than the LLOQ, the mean concentration value will be set to below the LLOQ in tables.

5.6 Sample Reprocessing

Samples may be reanalyzed in accordance with the standard operating procedure at the bioanalytical laboratory. If an observed concentration value represents an unexplained, significant deviation from the temporal consistency with the prior and following samples in the affected subject's concentration-time profile, the CP scientist may issue a request for sample reprocessing. Sample reprocessing will only be done if sufficient sample volume exists and if the stability of the sample is adequate.

6 SCHEDULE OF INTENDED ANALYSIS AND DEPENDENCIES

Final data analyses will be performed after the clinical database has been locked, the bioanalytical data has been quality assured, and the data has be transferred to BioMarin Clinical Pharmacology.

7 PHARMACOKINETIC PARAMETER ANALYSIS METHODS

7.1 Software

PK Parameter estimation and statistical analyses will be done using the current validated instance of Phoenix WinNonlin (version 6.4, Certara L.P., St. Louis, MO). Additional software may be used for data processing and graphing including R (version 3.4.1 or later), The R Foundation for Statistical Computing, Vienna, Austria) with R Studio version (1.1.423, or later, R Studio, Inc., Boston, MA).

7.2 Population(s) to be Analyzed

All subjects who receive a dose of BMN 111 and have measurable concentration values, for whom the primary PK data are considered to be sufficient and interpretable, will be included in the PK analysis.

7.3 Pharmacokinetic Parameter Analysis Methods

Estimates of the following PK parameters will be obtained and additional PK parameters may be estimated as deemed appropriate by the analyst.

T_{max}	Time to reach maximum observed post-dose concentration
C_{max}	Maximum observed post-dose concentration
AUC_{0-t}	Area under the plasma concentration-time curve from 0 to the time of last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, where C_t is the

	last measurable concentration and λ_z is the terminal elimination rate constant
$t_{1/2}$	Terminal half-life
CL/F	Apparent clearance, calculated as Dose/$AUC_{0-\infty}$ where F is absolute bioavailability
V_z/F	Volume or apparent volume of distribution, calculated as (CL/F)/λ_z

AUC_{0-t} will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.

Linear Trapezoidal Rule

$$AUC\Big|_{t_1}^{t_2} = \delta t \times \frac{C_1 + C_2}{2}$$

Logarithmic Trapezoidal Rule

$$AUC\Big|_{t_1}^{t_2} = \delta t \times \frac{C_2 - C_1}{\ln\left(\frac{C_2}{C_1}\right)}$$

where is δt is (t_2-t_1) and t is time and C is concentration.

7.4 Requirements for PK Parameter Reporting:

7.4.1 C_{max} and T_{max}

- If two peak concentrations of equal magnitude occur, the first peak and its corresponding timepoint will be reported as C_{max} and T_{max} respectively.

7.4.2 Lambda Z derived Parameters ($AUC_{0-\infty}$, $t_{1/2}$, λ_z, V_z/F, CL/F)

- The terminal elimination rate constant λ_z will initially be estimated using the best fit default method in Phoenix WinNonlin. The plots can then be analyzed by visual inspection to assess the quality of the estimation. If any of the conditions below are met then any parameter dependent on λ_z for computation (e.g., $t_{1/2}$, $AUC_{0-\infty}$) and λ_z should not be included in descriptive statistics and statistical testing procedures:

- If the coefficient of determination (R-squared) is less than 0.800
- If AUC extrapolation >20 %
- If less than 3 quantifiable concentrations-time values included in the regression of the terminal phase. C_{max} should not be used in the determination of λ_z.

7.5 Statistical Analysis Methods

All evaluable PK concentrations that were sampled within the protocol specified time windows and were not excluded or deemed and outlier, will be included in the summary statistics. PK concentrations will be summarized using nominal time. For descriptive statistics of concentration data, BLQ values will be treated as zero. Statistics presented will include sample size (n), mean, standard deviation (SD), minimum, median, maximum, and coefficient of variation (%CV). Mean, median, SD and CV% will not be reported when n is < 3.

All PK parameters that were not excluded or flagged as unreliably calculated will be included in the summary statistics. PK concentrations that were excluded from summary statistics will be documented in an exclusion table.

7.6 Suggested Tables and Figures

7.6.1 Tables

- Individual PK parameters
- Summary statistics of concentrations by nominal time for each analyte and treatment
- Summary statistics of PK parameters by treatment
- PK concentration-time data that was excluded from NCA

Additional tables may be generated as deemed appropriate.

7.6.2 Figures

- Individual plasma concentration vs. time profiles by treatment and analyte
- Mean plasma concentration (Mean ± SD) versus nominal time profiles by treatment

Additional figures may be generated as deemed appropriate by the analyst.

8 PHARMACOKINETIC / PHARMACODYNAMIC ANALYSIS

If supported by the data, the exposure-response relationship between BMN 111 exposure and immunogenicity, efficacy, biomarker, and safety PD endpoints of interest will be explored. The PD endpoints examined may include changes in annualized growth velocity (AGV), urine cGMP and serum BSAP biomarkers, heart rate (HR), blood pressure (BP), and incidences of injection site reactions (ISRs) and hypotension. Additional PD endpoints may be evaluated if deemed appropriate by the analyst.

8.1 Software

Data processing, graphics, and statistical modeling will be done using R (version 3.4.1 or later), The R Foundation for Statistical Computing, Vienna, Austria) with R Studio version (1.1.423, or later, R Studio, Inc., Boston, MA)

8.2 Population(s) to be Analyzed

All subjects who were administered a dose of BMN 111 and provided evaluable and interpretable PK and PD assessments with be included in the PK/PD analysis dataset.

8.3 Analysis Methods

Potential Correlations between BMN 111 and PD endpoints of interest will be explored graphically. Statistical modeling may then be used to further explore exposure-response correlations identified with the graphical analysis.

8.4 Summary Methods

Descriptive statistics of BMN 111 exposure by PD endpoint may be calculated and will include sample size (n), mean, standard deviation (SD), minimum, median, maximum, and coefficient of variation (%CV).

8.5 Suggested Tables and Figures

8.5.1 Tables

- PD endpoints used in PK/PD analyses by individual subject
- Summary statistics of BMN 111 exposure by PD endpoint for categorical endpoints
- Summary tables for any statistical models used

8.5.2 Figures

- Distribution plots of BMN 111 exposure by PD endpoints for categorical endpoints
- Scatter plots of BMN 111 exposure by PD endpoint for continuous endpoints
- Summary figures for any statistical models used

Additional tables and figures may be generated as deemed appropriate by the analyst.

9 QUALITY CONTROL

Quality control review of the PK analysis and report will be performed according to WI-114791 *Guidelines for Conducting Noncompartmental Analysis*.

10 REFERENCE

1. SOP-103648 *Phoenix WinNonlin Data Processing Through the Phoenix Platform*

2. SOP-104400 *Preparing a Clinical Pharmacology report*