Official Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with Achondroplasia

NCT Number: NCT03197766

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 01 February 2019

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with Achondroplasia
Protocol Number:	111-301
Active Investigational Product:	BMN 111 (modified rhCNP)
IND Number:	111299
European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2015-003836-11
Indication:	Achondroplasia
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 3
Sponsor's Responsible Medical Monitor:	PI , MD PI BioMarin UK LTD 10 Bloomsbury Way London WC1A 2SL
Treatment Duration:	52 weeks
Duration of Subject Participation:	60 weeks
Dose:	BMN 111 15 µg/kg or placebo daily
Study Population:	Children with achondroplasia
Date of Original Protocol:	1 September 2016
Date of Amendment 1	28 November 2016
Date of Amendment 2	27 April 2017
Date of Amendment 3	05 January 2018
Date of Amendment 4	01 February 2019

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 4

Date: 01 February 2019

RATIONALE AND SUMMARY OF MAJOR CHANGES

This protocol is being revised to make the following changes:

1. The following exploratory objectives have been moved to secondary

- Evaluation of change from baseline in body proportion ratios of the extremities [§8.0, Synopsis, and additional appropriate sections].
- Evaluation of the effect of BMN 111 on bone morphology/quality by X-ray and dual X-ray absorptiometry (DXA) [§8.0 and additional appropriate sections].
- Evaluate potential changes in health-related quality of life (HRQoL) and functional independence as measured by quality of life questionnaires [§8.0 and additional appropriate sections].

  Rationale: Due to the importance of clinical, morbidity, and HRQoL outcomes in achondroplasia, all clinical outcome endpoints (with the exception of optional assessments) have been moved from exploratory to secondary.

2. Description of contraception in the study inclusion criteria (§9.3.1 and additional appropriate sections) and birth control during and after the study (§9.3.3) have been updated.

Rationale: To provide clarity on requirements for the use of highly effective methods used in female participants and acceptable methods in male participants, and to define true abstinence to clarify when it is considered an acceptable method of contraception. This is in line with the Clinical Trial Facilitation Group "Recommendations related to contraception and pregnancy testing in clinical trials."

3. Duration of Subject Participation updated (§9.3.6 and additional appropriate sections) to 4-week safety follow-up after Week 52.

Rationale: Follow-up after the study has been extended to ensure adequate passage of time before the final safety follow-up so that potentially drug-related AEs should have already occurred

4. Primary and secondary efficacy variables separated so that new secondary variables are incorporated (§9.12.2 and additional appropriate sections).

Rationale: This change made to support Rationale 1.

5. Move selected exploratory objectives to be new secondary objectives (Synopsis, §9.12.3, and additional appropriate sections).

Rationale: This change made to support Rationale 1.

6. Exploratory efficacy variables deleted from §9.12.4 and moved to secondary efficacy variables (§9.12.3).

Rationale: This change made to support Rationale 1.

7. Change medical monitor from PI PI MD, PhD to PI , MD.
8. Replace “18 years of age” with “age of majority” (§5.3, §12 and additional appropriate sections).

Rationale: The age of majority varies by country.

9. Inserted “In Japan, subject enrollment will be staggered initially, with a minimum of a 2-week window between the first 4 subjects enrolled” in Study Design and Plan in Synopsis and §9.1.

Rationale: This measure was taken in Japan and implemented in a country-specific protocol given the limited exposure experience of Japanese subjects to BMN 111 at the time of the 111-301 study. The sponsor has now consolidated into one global protocol.

10. Removed “plasma DNA” in §9.12.4.4.

Rationale: DNA is not obtained from plasma

11. Administrative changes have been made throughout the amended protocol for consistency, accuracy, and clarity.

2 SYNOPSIS

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 **NAME OF FINISHED PRODUCT:** BMN 111 **NAME OF ACTIVE INGREDIENT:** Modified rhCNP	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE OF STUDY:

A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with Achondroplasia

PROTOCOL NUMBER:

111-301

STUDY SITES:

Approximately 33 clinical centers worldwide

PHASE OF DEVELOPMENT:

Phase 3

STUDY RATIONALE:

Achondroplasia (ACH), the most common form of disproportionate short stature or dwarfism, is an autosomal dominant genetic skeletal disorder caused by a gain-of-function mutation in the fibroblast growth factor receptor-3 gene (FGFR3), a negative regulator of endochondral bone formation. Due to this FGFR3 mutation, there is exaggerated negative regulation on endochondral ossification, which results in ACH (Laederich, 2010).

The use of modified recombinant C-type natriuretic peptide (rhCNP) as a potential therapy for the treatment of ACH is based on the mechanism of action of C-type natriuretic peptide (CNP). CNP and its receptor, NPR-B, are key regulators of skeletal growth. CNP binding to its receptor, natriuretic peptide receptor-B (NPR-B), acts as a key regulator of longitudinal bone growth by down-regulating the mitogen-activated protein kinase (MAPK) pathway. CNP-mediated activation of NPR-B results in the rescue of the dwarfism phenotype of mice with a FGFR3 gain-of-function mutation (Yasoda, 2004; Yasoda 2009). The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ model (Lorget, 2012,), and a mild [Ach] /+ model. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. Additionally, in wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically-tolerated dose levels (Wendt, 2015,). Therefore, administration of CNP has been proposed as a therapeutic approach for ACH.

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BioMarin has engineered a CNP analog (BMN 111) that has a longer half-life than endogenous CNP, thereby allowing daily subcutaneous (SC) administration. Similar to CNP, BMN 111 activates NPR-B signaling with subsequent inhibition of FGFR3 downstream signaling, leading to the promotion of chondrocyte proliferation and differentiation and subsequent increased endochondral bone formation. BMN 111 administration has been shown to promote endochondral bone formation at hemodynamically tolerated dose levels in both normal animals and mouse models of ACH reported (refer to current Investigators Brochure for additional information).

Human studies to date have demonstrated that BMN 111 is safe and well-tolerated at doses that result in improvements in growth velocity approaching that of children of average stature.

Study 111-101 was a Phase 1 double-blind, placebo-controlled study to assess the safety and tolerability of BMN 111 in healthy adult male volunteers without ACH. Part 1 examined a series of single subcutaneous doses (5 µg/kg, 10 µg/kg and 15 µg/kg), and Part 2 included 10 days of either fixed dosing or dose escalation (0.5 µg/kg to 8 µg/kg). BMN 111 was generally well tolerated at all doses. As expected, mild, transient, self-limited hypotension was reported (refer to current Investigators Brochure for additional information). BMN 111 demonstrated dose-related linear increases in exposure by maximum observed plasma concentration (C_{max}) (from 2.5 µg/kg to 15 µg/kg) in healthy volunteers; plasma elimination half-life ($t_{1/2}$) ranged from 30.7 to 140 minutes.

Study 111-202 was a Phase 2, open-label, sequential cohort, dose escalation study that assesses daily SC BMN 111 in pediatric subjects with ACH, starting with a dose of 2.5 µg/kg and escalating through additional dose cohorts up to 30 µg/kg. The primary objective of Study 111-202 was to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months; the secondary objectives were to determine change from baseline in annualized growth velocity (AGV), growth parameters, body proportions, and evaluate the dose-exposure and pharmacokinetic (PK) profiles of BMN 111 in children with ACH.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at the doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated at all dose levels (refer to current Investigators Brochure for specific details).

Analysis of efficacy data from the 6-month initial phase of Study 111-202 demonstrated a positive dose-dependent response in mean change from baseline AGV at doses ranging from 2.5-15 µg/kg daily. Subjects treated with 30 µg/kg daily also showed similar improvement in AGV after 6 months compared with subjects treated with 15 µg/kg daily. Safety data for the 30-µg/kg daily dose was also similar to the 15-µg/kg daily dose. Given that no clinically significant difference could be identified between the 15-µg/kg and 30-µg/kg daily dose in the Phase 2, 6-month safety and efficacy data, the lower of the two doses has been chosen for this Phase 3 study.

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Study 111-301 is designed to further characterize and confirm efficacy and safety of BMN 111 at 15 µg/kg for 52 weeks. This 60-week study (up to 4 weeks of screening, 52 weeks of treatment with an additional 4 weeks of safety follow up) will allow for assessment of the effect of daily BMN 111 administration on change from baseline in AGV, height, and body proportions in subjects treated with BMN 111 compared with control subjects in the placebo group, as well as further characterize safety and tolerability of BMN 111 in children with ACH. Additional endpoints will also be examined to determine the effect of BMN 111 on bone physiology and to assess quality of life and daily function of study subjects.

OBJECTIVES:

The primary objective of the study is to:

- Evaluate change from baseline in annualized growth velocity at 52 weeks in subjects treated with BMN 111 compared with control subjects in the placebo group.

The secondary objectives of the study are to:

- Evaluate change from baseline in height Z-score in subjects treated with BMN 111 compared with control subjects in the placebo group at 52 weeks.
- Evaluate change from baseline in upper:lower segment body ratio in subjects treated with BMN 111 compared with control subjects in the placebo group at 52 weeks.
- Evaluate change from baseline in body proportion ratios of the extremities.
- Evaluate effect of BMN 111 on bone morphology/quality by X-ray and dual X-ray absorptiometry (DXA).
- Evaluate potential changes in health-related quality of life (HRQoL) as measured by the Quality of Life in Short Stature Youth (QoLISSY) and the Pediatric Quality of Life Inventory (PedsQL) questionnaires.
- Evaluate potential changes in functional independence as measured by the Functional Independence Measure (WeeFIM) clinician-reported outcome.
- Evaluate safety and tolerability of BMN 111 in children with ACH.
- Evaluate the PK of BMN 111.
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures.
- Evaluate change from baseline in bone metabolism biomarkers.

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The exploratory objectives of the study are to:

- Evaluate sleep study scores by polysomnography in a subset of subjects.
- Evaluate biomarkers of BMN 111 activity.
- Evaluate genomic biomarkers.

STUDY DESIGN AND PLAN:

This is a Phase 3 randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of BMN 111 on growth velocity in children with ACH. Subjects who are 5 to < 18 years old, with documented ACH confirmed by genetic testing will have been enrolled in Study 111-901 for at least a 6-month period immediately before study entry, and meet all study eligibility criteria will participate. At least 110 eligible subjects will be stratified based on sex and Tanner stage (Stage 1, and > Stage 1, with no more than 20% of subjects > Tanner Stage 1) at Screening, and randomly assigned in a 1:1 ratio to one of two treatment groups: placebo or BMN 111 at 15 µg/kg/day. To achieve gender balance, approximately 50% of each gender will be enrolled, with neither to exceed 55%. In Japan, subject enrollment will be staggered initially, with a minimum of a 2-week window between the first 4 subjects enrolled.

For both placebo and BMN 111, the route of administration is subcutaneous injection and the frequency is daily. Approximately 33 clinical centers worldwide will participate in the study.

Safety monitoring will be conducted for all subjects randomized to BMN 111 or placebo after the first dose of BMN 111 or placebo is received and over the duration of the study. This will include a minimum of 2 hours post-dose observation on the first 3 days of dosing (and 30 minutes for all other days of dose administration) in conjunction with caregiver training for BMN 111 or placebo administration and adverse event (AE) documentation/reporting. It is generally expected that after subjects are tolerating BMN 111 or placebo well and specified criteria have been met (refer to Study Reference Manual), caregivers will begin administering BMN 111 or placebo at home. If the caregiver is unable or unavailable to administer BMN 111 or placebo, home health care may be provided. Contact by a study staff member to the caregiver will be required every 4 weeks (± 10 days) to all study subjects after the Week 6 visit when there are no study visits or contact in the preceding 4 weeks. During these contacts, study staff will ask about dose administration and seek information on AEs and SAEs by specific questioning. Information on all AEs and serious adverse events (SAEs) should be recorded in the subject's medical record and on the AE eCRF.

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After subjects have completed the treatment period of the study, those in both treatment and control groups may be eligible to receive BMN 111 in the extension study 111-302, to assess safety and efficacy of BMN 111 over a longer time period. Subjects will have the option to enroll in 111-302 after the Week 52/Study Completion Visit. Week 52 assessments will serve as Baseline assessments for entry to study 111-302 if the visit occurs on the same day or within 2 weeks. Subjects who enroll into 111-302 more than 2 weeks after the 111-301 Week 52 visit will have a separate Baseline visit; the same assessments as those performed at Week 52 will be repeated at that time.

Data Monitoring Committee

In addition to safety monitoring by BioMarin personnel, an independent data monitoring committee (DMC) will review and provide input on the safety data collected in the study. DMC data review will occur at regular time periods during the course of the study (or ad hoc, if indicated) as outlined in a separate DMC charter.

NUMBER OF SUBJECTS PLANNED:

At least 110 subjects with ACH, as documented by clinical grounds and genetic testing.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Parent(s) or guardian(s) are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, subjects under the age of majority are willing and able to provide written assent (if required by local regulations or the IRB/EC) after the nature of the study has been explained and prior to performance of any research-related procedure. Subjects who reach the age of 18 years while the study is ongoing will be asked to provide their own written consent.
2. 5 to < 18 years old at study entry.
3. Have ACH, documented by clinical grounds and confirmed by genetic testing.
4. Have at least a 6-month period of pretreatment growth assessments, including standing height, and are currently active participants in 111-901.
5. Females ≥ 10 years old or who have begun menses must have a negative pregnancy test at the Screening Visit and be willing to have additional pregnancy tests during the study.
6. If sexually active, willing to use contraception as specified in Section 9.3.3
7. Are ambulatory and able to stand without assistance.

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8. Are willing and able to perform all study procedures.
9. Caregivers are willing to administer daily injections to the subjects and complete the required training.

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Have hypochondroplasia or short stature condition other than ACH (eg, trisomy 21, pseudoachondroplasia).
2. Have any of the following:
    - Hypothyroidism or hyperthyroidism.
    - Insulin-requiring diabetes mellitus.
    - Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others).
    - Inflammatory bowel disease.
    - Autonomic neuropathy.
3. Have a history of any of the following:
    - Renal insufficiency defined as serum creatinine > 2 mg/dl.
    - Chronic anemia.
    - Baseline systolic blood pressure (BP) < 70 millimeters of mercury (mm Hg) or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms ie, dizziness, fainting) or recurrent symptomatic orthostatic hypotension.
    - Cardiac or vascular disease, including the following:
        - Cardiac dysfunction (abnormal echocardiogram) at Screening Visit.
        - Hypertrophic cardiomyopathy.
        - Pulmonary hypertension.
        - Congenital heart disease.
        - Cerebrovascular disease.

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- Aortic insufficiency or other clinically significant valvular dysfunction.
- Clinically significant atrial or ventricular arrhythmias.

4. Have a clinically significant finding or arrhythmia on screening electrocardiogram (ECG) that indicates abnormal cardiac function or conduction or QTc-F > 450 msec.
5. Have an unstable condition likely to require surgical intervention during the study (including progressive cervical medullary compression or severe untreated sleep apnea).
6. Evidence of decreased growth velocity (AGV < 1.5 cm/year) as assessed over a period of at least 6 months or of growth plate closure (proximal tibia, distal femur) through bilateral lower extremity X-rays including both AP and lateral views.
7. Documented Vitamin D deficiency (concentration of blood 25-hydroxy-vitamin D <12 ng/mL or <30 nmol/L).
8. Require any investigational agent prior to completion of study period.
9. Have received another investigational product or investigational medical device within 6 months before the Screening Visit.
10. Have used any investigational product or investigational medical device for the treatment of ACH or short stature at any time, including BMN 111.
11. Current therapy with antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, GnRH agonists, any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function (Table 9.3.2.1).
12. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the previous 6 months or treatment greater than 6 months at any time.
13. Have had > 1 month treatment with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the previous 12 months.
14. Planned or expected to have limb-lengthening surgery during the study period. Subjects with previous limb-lengthening surgery may enroll if surgery occurred at least 18 months prior to screening and healing is complete without sequelae.

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15. Planned or expected bone-related surgery (ie, surgery involving disruption of bone cortex, excluding tooth extraction), during the study period. Subjects with previous bone-related surgery may enroll if surgery occurred at least 6 months prior to screening and healing is complete without sequelae.
16. Have had a fracture of the long bones or spine within 6 months prior to screening.
17. Pregnant or breastfeeding at the Screening Visit or planning to become pregnant (self or partner) at any time during the study.
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at least 3 × upper limit of normal (ULN) or total bilirubin at least 2 × ULN (except for subjects with known history of Gilbert's disease).
19. History of severe untreated sleep apnea.
20. Have had new initiation of sleep apnea treatment (eg, continuous positive airway pressure [CPAP] or sleep apnea-mitigating surgery) in the previous 2 months prior to screening.
21. Have current malignancy, history of malignancy, or currently under work-up for suspected malignancy.
22. Have known hypersensitivity to BMN 111 or its excipients.
23. Have a history of hip surgery or hip dysplasia atypical for achondroplasia subjects.
24. Have clinically significant hip injury in the 30 days prior to screening.
25. History of slipped capital femoral epiphysis or avascular necrosis of the femoral head.
26. Are unable to lie flat when in prone position (needed for hip exam).
27. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the investigator.
28. Concurrent disease or condition that, in the view of the investigator, would interfere with study participation or safety evaluations, for any reason.
29. Have a condition or circumstance that, in the view of the investigator, places the subject at high risk for poor treatment compliance or for not completing the study.

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INVESTIGATIONAL PRODUCT(S), DOSE, ROUTE AND REGIMEN:

For subjects randomized to BMN 111, the clinical drug product will be supplied in sterile, single-dose, Type I glass vials with coated stopper and flip-off aluminum cap. BMN 111 drug product is supplied as 0.8-mg or 2-mg lyophilized, preservative-free, white to yellow powder for reconstitution with commercially-sourced sterile water for injection (WFI). The reconstituted solution is colorless to yellow and contains 0.8 mg/mL to 2 mg/ml of BMN 111, as well as citric acid, sodium citrate, trehalose, mannitol, methionine, polysorbate 80, and sterile WFI. The target pH of the reconstituted solution is 5.5.

All reconstitution and dose preparation steps should be performed as indicated in the Study Drug Injection Guide and Injection instruction media.

BMN 111 will be administered as a single SC daily dose of 15 µg/kg. BMN 111 will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Subjects will be observed for 2 hours after the injection for Days 1 to 3, and 30 minutes for all other dosing administration days.

REFERENCE THERAPY(IES), DOSE, ROUTE AND REGIMEN:

BMN 111 placebo lyophilized product will be supplied in sterile, single-dose, Type I glass vials with coated stopper and flip-off aluminum cap. The placebo is designed to be comparable in appearance to the drug product and contains all of the components of the drug product except the drug substance.

All reconstitution and dose preparation steps should be performed as indicated in the Study Drug Injection Guide and Injection instruction media.

Placebo will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Subjects should be observed for 2 hours after the injection for Days 1 to 3, and 30 minutes for all other dosing administration days.

DURATION OF TREATMENT:

52 weeks

CRITERIA FOR EVALUATION:

Primary Efficacy:

Primary efficacy will be assessed by change from baseline in height growth velocity (annualized to cm/yr).

Safety:

Safety will be evaluated by assessment of AEs, SAEs, laboratory test results (urinalysis, chemistry, hematology), changes in vital signs, physical examination, ECG, X-ray/DXA assessments of bone morphology and quality, clinical hip assessment, anti-BMN 111 immunogenicity assessments; salivary cortisol, serum prolactin, and follicle stimulating hormone (FSH)/luteinizing hormone (LH) levels (FSH/LH will be monitored for all subjects >8 years of age, and for subjects at Tanner stage 2, whichever is earlier); and cognitive assessment with the Childhood Behavioral Checklist (CBCL). Additional assessments will be conducted to evaluate changes from baseline in bone metabolism.

Pharmacokinetics:

PK sampling will be carried out over the 12-month study period in subjects randomized to BMN 111 or placebo. If supported by the data, the PK variables to be calculated for subjects randomized to BMN 111 will include:

- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$).
- Area under the plasma concentration-time curve from time 0 to the time of last measurable concentration (AUC_{0-t}).
- Maximum observed plasma concentration (C_{max}).
- Time to reach C_{max} (T_{max}).
- Elimination half-life ($t_{1/2}$).
- Apparent clearance (CL/F).
- Apparent volume of distribution (V_z/F).

All PK variables will be estimated by non-compartmental analysis.

Secondary:

Secondary assessments will include change from baseline in growth parameters (height), body proportions of the upper and lower segments, and proportions of the extremities by anthropometry. Growth parameters will be assessed by height Z-scores. Body proportions will be assessed by anthropometric measurements and measurement ratios. Anthropometric measurements may include but are not limited to standing height; sitting height; weight; head circumference; upper and lower arm length; leg length; and arm span. Measurement ratios may include, but are not limited to, upper:lower body segment ratio, upper arm:forearm length ratio, upper leg:lower leg length ratio, and arm span:standing height ratio. Further details are provided in the Study 111-301 Anthropometric Measurement Guidelines.

Health-related quality of life and functional independence will be assessed using the QoLISSY, PedsQL, and WeeFIM (reference Training Materials for specifics).

Exploratory:

Polysomnography will be conducted to evaluate sleep apnea in a subset of subjects. Additional

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exploratory assessments will be conducted to evaluate changes from baseline in BMN 111 activity biomarkers and optional genomic biomarkers will be evaluated.

STATISTICAL METHODS:

Sample Size Determination:

With 55 subjects planned in each of the two randomized groups (one BMN 111 group and one placebo group), the power to detect a difference of 1.75 cm/year between the BMN 111 group and the placebo group in change from baseline in AGV at 12 months is approximately 90%, assuming that the pooled standard deviation of the change from baseline in AGV is 2.80, using a two-sided two-sample t-test at a 0.05 significance level. The power calculation is based on data from Study 111-202 (a phase 2, open-label, sequential cohort dose-escalation study) and Study 111-901 (a natural history study for pediatric subjects with achondroplasia).

Efficacy Analysis:

Efficacy analysis will be carried out for the 52-week (12-month) period. Efficacy analysis will be based on all randomized subjects who receive at least one dose of double-blinded BMN 111 or placebo in this study.

The primary efficacy endpoint is the change from baseline in AGV at the 12-month time point based on standing height measures. The details of the derivation for AGV are provided in Section 14.2.1. The AGV and its change from baseline at each scheduled post-treatment visit will be summarized using descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum) per group. The primary estimand is the difference in mean change from baseline in AGV at the 12-month time point between the BMN 111 group and the placebo group. The estimand is defined on all randomized subjects who received at least one dose of double-blinded BMN 111 or placebo.

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Subjects who discontinue from the study drug will be encouraged to remain in the study, and their non-missing height measurements will continue to be used in calculating the AGV and to be included in the analysis per intend to treat principle. In the event that missing data does occur despite all efforts, missing standing height will be imputed based on multiple imputation (MI) with pattern-mixture models (Little 1993; Molenberghs 2007,) implemented in Proc MI of SAS where the missing, unobserved observations of the standing height are assumed to follow missing not at random (MNAR) mechanism. For each imputation, the standing heights collected from the subjects in the same randomization group who also discontinue treatment prematurely (but remain in the study), referred to as off-treatment data, will be used as the reference data for MI. Ten (10) sets of imputations of the missing standing heights will be constructed from MI and the AGV at the 12-month time point will be calculated based on these 10 sets of data. For each subject whose value is imputed, the 10 imputed values will be provided in a data listing that will be included in the appendix of the CSR.

The primary null hypothesis of no difference between the BMN 111 group and the placebo group in the mean change from baseline in AGV at the 12-month time point will be tested based on an analysis of covariance (ANCOVA) model, with fixed-effect terms including treatment group, sex, and Tanner stage, and age and the baseline AGV as covariates. The above-mentioned ANCOVA model will be applied to the 10 imputed data sets from MI. The analysis results based on the 10 imputed datasets will be summarized using Proc MIANALIZE in SAS.

The key secondary efficacy endpoints are the change from baseline in height Z-score, and the change from baseline in upper:lower body segment ratio. The estimand of the key secondary efficacy endpoints is the difference in mean change from baseline in the corresponding endpoint at the 12-month time point between the BMN 111 group and the placebo group (all randomized subjects who received at least one dose of double-blinded BMN 111 or placebo). The measurement of standing height at each scheduled visit will be converted to age-and sex-appropriate standard score, also referred to as Z-score, by comparison with normal reference standards (not ACH). The height Z-score and its change from baseline will be summarized using descriptive statistics. Any missing observations will be imputed based on MI with pattern-mixture models described above. The null hypothesis of no difference between the BMN 111 group and the placebo group in the mean change from baseline in the height Z-score at the 12-month time point will be tested based on 10 imputed data sets using an analysis of covariance (ANCOVA) model, with fixed-effect terms including treatment group, sex, and Tanner stage, and age and the baseline Z-score as covariates. The analysis results based on the 10 imputed datasets will be summarized using Proc MIANALIZE in SAS. The change from baseline in upper:lower body segment ratio at the 12-month time point will be similarly summarized and tested.

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The overall type I family-wise error rate for testing the primary and secondary efficacy endpoints will be controlled at the 0.05 significance level using the following 3-step serial gatekeeping multiple comparisons procedure (MCP). Following this MCP, advancement to the next step will only occur if the null hypotheses within a step and the previous step(s) are all rejected at the significance level of 0.05 in favor of BMN 111. If any null hypotheses within a step is not rejected or is rejected but not in favor of BMN 111, the hypothesis tests corresponding to all subsequent steps will not be considered statistically significant. All hypothesis tests will be two-sided.

1. The first step will be the test comparing the BMN 111 group to the placebo group for the primary efficacy endpoint, the change from baseline in AGV at 12-month time point. If the null hypothesis is not rejected (ie, p-value > 0.05) or is rejected but not in favor of BMN 111, all subsequent statistical tests will not be considered statistically significant. The study is considered positive if the primary test is significant in favor of BMN 111.
2. The second step will be the test comparing the BMN 111 group to the placebo group for the secondary efficacy endpoint, the change from baseline in height Z-score at 12-month time point. If the null hypothesis is not rejected (ie, p-value > 0.05) or is rejected but not in favor of BMN 111, the subsequent statistical test will not be considered statistically significant.
3. The third step will be the test comparing the BMN 111 group to the placebo group for the secondary efficacy endpoint, the change from baseline in upper:lower body segment ratio at 12-month time point at a significance level of 0.05.

Additional secondary efficacy analyses will also include change from baseline in body proportions of extremities, and HRQoL and functional independence assessments.

Change in body proportions of extremities will be assessed by anthropometry.

To assess the robustness of the primary analysis result, sensitivity analyses such as the following will be performed:

Mixed Model with Repeated Measures (MMRM)

The primary null hypothesis of no difference between the BMN 111 group and the placebo group in the mean change from baseline in AGV at the 12-month time point will be tested based on all available AGV assessments from all scheduled visits using a mixed model with repeated measures (MMRM), with fixed-effect terms including treatment group, visit, sex, Tanner stage, and interaction of treatment group and visit, and age and the baseline AGV as covariates, repeated over visits.

MI Based on Missing At Random (MAR) Assumption

The sensitivity analyses will be based on the MI technique as proposed by Little and Rubin (1987) implemented in PROC MI of SAS where the missing, unobserved observations of the response variable are assumed to follow MAR mechanism. The MI procedure will be directly applied to standing height and AGV will be calculated based on imputed height. The ANCOVA model described in the primary analysis will be performed separately for each imputation dataset and a summary overall imputed samples will be provided for each analysis.

Random Coefficients Model

The mean change from baseline in height at 12-month time point will be estimated for both the treatment group and the placebo group based on a MMRM, with fixed-effect terms including treatment group, visit, sex, Tanner stage, and age and the baseline height as covariates, and random-effect terms of the intercept and the subject × visit interaction. For each randomized group, an AGV at 12-month time point will be defined as the mean change from baseline in height at 12-month from the MMRM model above.

ANCOVA on Completers

In this sensitivity analysis, the estimand will be the difference of the means of the change from baseline in AGV at 12-month observed from subjects who have non-missing observation at 12-month between the two randomized groups. The LS means of the change from baseline in AGV at 12-month will be estimated for both the randomized groups based on the ANCOVA model described in the primary analysis. In this analysis, only subjects with observed AGV change from baseline at 12-month will be included. No extrapolation or imputation will be performed for missing 12-month or Day 1 standing height measurements.

Similar sensitivity analyses may also be performed on secondary efficacy endpoints. Subgroup analyses on the efficacy endpoints based on Tanner stage or age groups may also be performed. By-subject listings will also be provided for efficacy endpoints. Detailed statistical methods will be provided in the SAP.

Safety Analysis:

All randomized subjects who receive at least one dose of double-blinded BMN 111 or placebo will be included in the study safety analysis. The safety analysis will be descriptive.

All AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) to assign system organ class and preferred term classification to event and disease, based on the original terms entered on the CRF. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment as assessed by investigator, and severity. All AEs, including SAEs and AEs that lead to permanent discontinuation from the study and from the study treatment, will be listed.

All other safety measures including X-ray/DXA assessments of bone morphology, quality, and growth of the extremities and spine (X-rays only), laboratory tests, CBCL assessments, vital signs, physical examination, ECG, clinical hip assessment, anti-BMN 111 immunogenicity, and bone

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metabolism biomarkers, will also be summarized descriptively by group, as appropriate. By-subject listings will be provided for these safety endpoints.

Pharmacokinetic Analysis:

In subjects randomized to the active treatment arm, PK parameters generated over the course of the study will be evaluated and summarized with descriptive statistical measures (mean, standard deviation, percentage of coefficient of variation [CV%], minimum, median and maximum). Correlative analyses of some of the PK parameters with efficacy, safety and immunogenicity measures may be conducted.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

µg/kg	microgram/kilogram
ACE	angiotensin-converting enzyme
Ach	Fgfr3G380R achondroplasia mouse model
ACH	achondroplasia
ADL	Activity of Daily Living
AE	adverse event
AGV	annualized growth velocity
ALT	alanine aminotransaminase
ANCOVA	analysis of covariance
ANP	atrial natriuretic peptide
AP	anterior-posterior
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMC	bone mineral content
BMD	bone mineral density
BNP	B-type Natriuretic Peptide
BP	blood pressure
BPV	BioMarin pharmacovigilance
°C	degree Celsius
CBCL	Child Behavior Checklist
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CL/F	Apparent clearance
C_{max}	maximum observed plasma concentration
CNP	C-type natriuretic peptide
CNP-53	C-type natriuretic peptide (53 amino acids in length)
CPAP	continuous positive airway pressure
CRA	clinical research associate
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CV%	percentage of coefficient of variation
DBP	diastolic blood pressure
DMC	data monitoring committee
DXA	dual X-ray absorptiometry

ECHO	echocardiogram
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOSI	Event(s) of special interest
ERK	extracellular signal-regulated kinase
EU	European Union
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FSH	follicle stimulating hormone
G380R	substitution in the transmembrane domain of the FGFR3 receptor at position 380
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPA	hypothalamic pituitary adrenal
HR	heart rate
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IP	investigational product
IRB	institutional review board
ISR	injection site reaction
IUD	intrauterine device
LH	luteinizing hormone
LS	least squares
LV	left ventricular
MAPK	mitogen-activated protein kinase
MAR	missing at random
MCP	multiple comparisons procedure
mg	milligram
MI	multiple imputation
mL	milliliter
msec	millisecond
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model with repeated measures
MNAR	missing not at random
NAb	neutralizing antibodies
NCI	National Cancer Institute

NEP	neutral endopeptidase
NP	natriuretic peptide
NPR-B	natriuretic peptide receptor type B
PA	posterior-anterior
PedsQL	Pediatric Quality of Life Inventory
PI	Principal Investigator
PK	pharmacokinetics
PRO	patient-reported outcome
REB	research ethics board
QoL	quality of life
QoLISSY	Quality of Life in Short Stature Youth
QT	a measure of the time between the start of the Q wave and the end of the T wave
QTc-F	Fridericia's corrected QT interval
rhCNP	recombinant C-type natriuretic peptide
SAEs	serious adverse events
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SDV	source document verification
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	elimination half-life
TAb	total antibody
T_{max}	time to reach C_{max}
ULN	upper limit of normal
US	United States
USA	United States of America
V_z/F	Apparent volume of distribution
WeeFIM	Functional independence measure for children
WFI	water for injection

Definition of Terms:

Investigational Product (IP):

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6]).

The terms "IP" and "study drug" may be used interchangeably in the protocol.

5 ETHICS

BioMarin Pharmaceutical Inc. (hereafter referred to as BioMarin or the Sponsor) conducts its studies according to the highest ethical and scientific standards. The following sections articulate standards to which investigators will be held accountable, as well as matters of compliance to document adherence to such standards.

5.1 Institutional Review Board or Independent Ethics Committee

Investigators are expected to interact with independent ethics committees (IECs) promptly, as required, during the course of the study. This includes, but is not limited to, providing appropriate documentation to support study initiation and maintaining appropriate flow of safety and other information during the course of the study and for study close-out activities. BioMarin (or designee) will assist investigators with access to timely and accurate information and with assurance of prompt resolution of any queries.

Prior to initiating the study, the investigator will obtain written confirmation that the institutional review board (IRB), IEC, or research ethic board (REB) is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to BioMarin Pharmaceutical Inc. (BioMarin) or its designee.

The investigator will provide the IRB/IEC/REB with all appropriate material, including, but not limited to, the protocol, Investigator's Brochure, Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated to the native language of the clinical site or to the language of the intended subject, if the subject speaks a language other than the native language.

The study will not be initiated and Investigational Product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the investigator and copies are received at BioMarin or its designee. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the study are made to the IRB/IEC/REB and BioMarin by the investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

It is expected that investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, providing eligible subjects for study enrollment; adhering to diagnostic or other procedures as specified in the protocol; and assuring appropriate compliance with study treatment administration and accountability.

This study will be conducted in accordance with the following:

- European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, for studies conducted within any European country.
- United States Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable.
- ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R2) (ICH E6 R2).
- The ethical principles established by the Declaration of Helsinki.

Specifically, this study is based on adequately performed laboratory and animal experimentation, and previous clinical data as well. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks. The rights and welfare of the subjects will be respected and the investigators conducting the study do not find the hazards to outweigh the potential benefits. Each subject, or his/her legally authorized representative will provide written, informed consent before any study-related tests or evaluations are performed.

5.3 Subject Information and Informed Consent

A properly written and executed informed consent form (ICF), in compliance with the Declaration of Helsinki, ICH E6 R2 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50 and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF (minor assent form and parental ICF for studies involving minors), and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

Subjects under the age of majority will provide written assent (if required), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects. The investigator will provide copies of the signed ICF to each subject (or the legally authorized representative of the subject) and will maintain the original in the record file of the subject.

During administration of informed consent, expectations regarding participation in the study should be made clear to subjects. Subjects who are not willing and/or are not able to comply with all aspects of the study should not be encouraged to participate.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the investigator at each site must provide to BioMarin or designee, a fully executed and signed United States (US) Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of subjects in this study.

The study will be administered by and monitored by employees or representatives of BioMarin. Clinical Research Associates (CRAs) or trained designees will monitor each site on a periodic basis and perform verification of source documentation for each subject as well as other required review processes. BioMarin's Pharmacovigilance Department (or designee) will be responsible for the timely reporting of SAEs to appropriate regulatory authorities as required.

In multicenter studies, a Coordinating Investigator will be identified who will be responsible for study oversight. The Coordinating Investigator will read the clinical study report (CSR) and confirm that it accurately describes the conduct and results of the study, to the best of his or her knowledge. The Coordinating Investigator will be chosen on the basis of active participation in the study, ability to interpret data, and willingness to review and sign the report in a specified timeframe. The identity of the Coordinating Investigator and a list of all investigators participating in the study will be provided in the CSR.

Clinical laboratory evaluations will be performed at central laboratories unless use of a local laboratory is clinically indicated in order to have expedited results. Assessment of pharmacokinetics (PK) and biomarkers will be conducted by BioMarin (or designee). Additional details and requirements will be provided in the Study Laboratory Manual.

7 INTRODUCTION

BMN 111 is a proposed pharmacologic therapeutic option for achondroplasia (ACH), the most common form of dwarfism.

ACH is a rare disease with a prevalence of 1/25000 in the US (Wynn, 2007). The average adult heights for men and women with ACH are 131 cm and 124 cm, respectively (Genetics Home Reference, 2012). Characteristic features include long and narrow trunk, a large head with frontal bossing, hypoplasia of the mid-face, bowed legs and stenosis of the foramen and spinal canals that can be life-threatening. Foramen magnum stenosis can lead to cervicomedullary compression in infants with complications including hydrocephalus, hypotonia, respiratory insufficiency, apnea, cyanotic episodes, feeding problems, quadriparesis, and sudden death.

There is no approved pharmacological therapy for achondroplasia in the United States of America (USA) or European Union (EU). Current treatments for achondroplasia are focused on neurosurgical interventions for foramen magnum stenosis or lumbar stenosis, thoracolumbar braces to help ameliorate the kyphosis, or limb lengthening requiring multiple operations over 2 to 3 years (Shirley, 2009); (Horton 2007).

ACH is caused by a gain-of-function mutation in fibroblast growth factor (FGF) R3, a negative regulator of chondrocyte proliferation and differentiation. The most common mutation (98%) in ACH patients is a G380R substitution in the transmembrane domain of FGFR3. The majority of new cases (80%) originate from parents of average stature.

The extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) pathway mediates part of FGFR3 inhibition of chondrocyte proliferation and differentiation (Foldynova-Trantirkova, 2012,). The ERK MAPK pathway is modulated by CNP, a positive regulator of chondrocyte proliferation and differentiation. Binding of CNP to the Natriuretic Peptide-Receptor B (NPR-B) antagonizes FGFR3 downstream signaling by inhibiting the MAPK (ERK1/2) pathway at the level of RAF-1 (Krejci, 2005,); (Yasoda, 2004,); (Yasoda, 2009,);(Pejchalova, 2007). This crosstalk was demonstrated in a mouse model of FGFR3-related chondrodysplasia (Yasoda, 2004,);(Yasoda, 2009,). The dwarfism phenotype of mice harboring the FGFR3G380R mutation was rescued by expression of C-type natriuretic peptide (CNP) in cartilage or by the continuous administration of CNP (infusion).

CNP is a member of the natriuretic peptide (NP) family that includes Atrial Natriuretic Peptide (ANP) and B-type Natriuretic Peptide (BNP). These peptides are structurally related but are distinct paracrine/autocrine (CNP) or endocrine (ANP and BNP) factors that regulate the cardiovascular (CV), skeletal, nervous, reproductive and other systems. Synthetic analogs

of ANP (anaritide and carperitide) and BNP (nesiritide) have been investigated as potential therapies for the treatment of decompensated heart failure and cardiovascular-related diseases.

BMN 111 is a 39-amino acid CNP analogue harboring the 37 amino acids of the human CNP53 C-terminal sequence and modified by the addition of two amino acids (Pro-Gly) on the N-terminus. It is a recombinant human peptide fused to human transcription factor (TAF) and expressed as an inclusion body in *E. coli*. BMN 111 is liberated and solubilized from the TAF-fusion protein by formic acid cleavage, and purified by column chromatography (Long, 2012,). BMN 111 was designed to 1) mimic CNP activities in terms of receptor binding and pharmacological activity and 2) be resistant to neutral endopeptidase (NEP) digestion in order to have an extended half-life in comparison to CNP that is presumed to increase exposure to the target growth plate (Wendt, 2015,).

A comprehensive review of BMN 111 is contained in the current version of the Investigator's Brochure supplied by BioMarin. Investigators are required to review the Investigator's Brochure prior to initiating this study.

7.1 Nonclinical Studies

The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ model (Lorget, 2012,), and a mild [Ach] /+ model. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. Additionally, in wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels (Wendt, 2015,).

BMN 111-related adverse findings in nonclinical species (mice, rats, cynomolgus monkeys) were limited to the known mechanism of action of CNP on the growth plate and vasculature. Reversible subcutaneous injection site reactions were reported, including injection site discoloration and microscopic findings of perivascular mononuclear cell infiltrates that were seen with slightly higher incidence and severity in BMN 111-treated rats and monkeys compared to the vehicle control. Adverse skeletal changes associated with exaggerated growth were seen in normal nonclinical species with open growth plates, and were dose-, exposure- and time-dependent. CBI [redacted]. Additional detailed information

about nonclinical studies of BMN 111 is provided in the current version of the Investigator's Brochure supplied by BioMarin.

7.2 Previous Clinical Studies

7.2.1 Study 111-101

Study 111-101, "A Phase 1, Two Part, Double Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of BMN 111 Administered to Healthy Adult Volunteers," was a first-in-human study conducted in 2 parts to allow for assessment of the safety, tolerability, and PK of BMN 111 administered as a single dose and as a multiple dose to healthy adult male volunteers.

Doses ranging from 5.0 µg/kg to 15.0 µg/kg were administered as a single SC dose; doses ranging from 0.5 µg/kg to 8.0 µg/kg were administered daily in the multiple ascending dose segment of the study. As expected, mild, transient, self-limited hypotension occurred. The majority of these cases were asymptomatic and observed upon assumption of an upright posture following recumbence. Hypotension events were reported in the BMN 111 treatment groups with higher frequency compared with placebo. All events were judged to be mild in severity and resolved spontaneously without an intervention. These events occurred across dose ranges. Due to the limited number of events at each dose, it is unclear if symptomatic hypotension is dose related. No dose limiting toxicities were identified outside of these cardiovascular findings. The only AEs occurring in more than one subject receiving BMN 111 were orthostatic hypotension, contact dermatitis, and back pain, and injection site reactions. Most AEs in the study were of mild severity, and no SAEs were reported. There were no AEs that led to premature discontinuation of study drug.

The PK parameters for BMN 111 were obtained from Part 1 of the study and from the first dose on Day 1 of the multiple dose study in Part 2. CBI [redacted]

CBI [redacted].

7.2.2 Study 111-202

Study 111-202 was a Phase 2, open-label, sequential cohort, dose escalation study that assesses daily SC administration of BMN 111 in pediatric subjects with ACH. The primary objective of Study 111-202 was to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months; the secondary objectives were to determine change from baseline in annualized growth velocity (AGV), growth parameters, body proportions, and evaluate the dose-exposure and PK profiles of BMN 111 in children with ACH.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at dose cohorts of 2.5, 7.5, 15, and 30 µg/kg (Cohorts 1 to 4, respectively) was generally well tolerated. The most common AEs were mild injection site reactions, pyrexia, asymptomatic hypotension, headache, and nasopharyngitis. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

Analysis of efficacy data from the 6-month initial phase of Study 111-202 demonstrated that the mean (standard deviation) change from baseline AGV when BMN 111 is administered at 2.5, 7.5, 15, and 30 µg/kg subcutaneously daily for 6 months is -0.37 (1.592), 1.28 (1.439), 2.01 (1.999), and 2.08 (2.137) cm/year, respectively. Thus, a positive dose-dependent response was observed in change from baseline AGV at doses ranging from 2.5-15 µg/kg daily.

In regards to 12-month data, subjects in Cohort 3 completed 12 months on a stable daily dose of 15 µg/kg and positive change from baseline in AGV was observed in subjects in Cohort 3. Subjects treated with 30 µg/kg daily also showed similar improvement in mean AGV after 6 months and their mean changes from baseline in AGV were similar to subjects treated with 15 µg/kg daily. Safety data for the 30 µg/kg daily dose was also similar to the 15 µg/kg daily dose. Thus, no clinically significant difference could be identified between the 15 µg/kg and 30 µg/kg daily dose in the Phase 2, 6-month safety and efficacy data.

Single-dose PK data from Day 1 showed BMN 111 was rapidly absorbed (median T_{max} between 5.00 and 16.0 minutes) and rapidly cleared from plasma (mean $t_{1/2}$ ranging from 24.4 to 27.0 minutes).

There was no evidence of accumulation with multiple daily dosing, and all pre-dose PK samples were below the limit of quantitation, consistent with the short half-life relative to the daily dosing regimen. Overall, exposure following multiple dosing was similar to exposure following single doses, and remained consistent through 24 months, indicating no apparent time-dependence in PK through 24 months of treatment.

Further details regarding results from the 111-202 study can be found in the current version of the Investigator's Brochure.

7.3 Ongoing Clinical Studies

7.3.1 Study 111-205

Study 111-205 is an ongoing open-label, Phase 2 extension study to assess long-term safety, tolerability, and efficacy of BMN 111 in children with ACH. Subjects continue receiving the same stable dose of BMN 111 received upon completion of the 111-202 study (up to 30 µg/kg daily). This 5-year study allows for long-term assessment of the effect of daily BMN 111 administration on safety, tolerability, growth velocity, height, and body proportions in subject completing 2 years of BMN 111 treatment in Study 111-202 (7 years total BMN 111 treatment duration). Additional exploratory endpoints are being examined to determine long-term effects of BMN 111 on bone physiology and the medical complications of ACH.

7.4 Study Rationale

BioMarin has engineered a CNP analog (BMN 111) that has a longer half-life than endogenous CNP, thereby allowing daily subcutaneous (SC) administration. Similar to CNP, BMN 111 activates NPR-B signaling with subsequent inhibition of FGFR3 downstream signaling, leading to the promotion of chondrocyte proliferation and differentiation and subsequent increased endochondral bone formation. BMN 111 administration has been shown to promote endochondral bone formation at hemodynamically tolerated dose levels in both normal animals and mouse models of ACH reported (refer to current Investigators Brochure for additional information).

Human studies to date have also demonstrated that BMN 111 is safe and well tolerated at doses that result in improvements in growth velocity approaching that of children of average stature.

Analysis of safety data from the Study 111-202 showed that treatment with BMN 111 was generally well tolerated at all dose levels (refer to current Investigators Brochure for specific details).

Analysis of efficacy data from Study 111-202 demonstrated that that subjects given BMN 111 at the dose of 15 µg/kg daily had a clinically significant improvement in AGV, with approximately ~50% increase over baseline seen with treatment for 6 months which was sustained after continued treatment for 12 months.

Subjects treated with 30 µg/kg daily also showed similar improvement in mean AGV after 6 months and their mean changes from baseline in AVG were similar to subjects treated with 15 µg/kg daily. Safety data for the 30-µg/kg daily dose was also similar to the 15-µg/kg daily dose. Given that no clinically significant difference could be identified between the 15 µg/kg and 30 µg/kg daily dose in the Phase 2, 6-month safety and efficacy data, the lower of the two doses has been chosen for this Phase 3 study.

Study 111-301 is designed to further characterize and confirm efficacy and safety of BMN 111 at a dose of 15 µg/kg for 52 weeks in a placebo-controlled study. This 60-week study (up to 4 weeks of screening, 52 weeks of treatment with an additional 4 weeks of safety follow up) will allow for assessment of the effect of daily BMN 111 administration on growth velocity, growth (height), and body proportions (lower:upper segments) in subjects treated with BMN 111 compared with the placebo group, as well as further characterize safety and tolerability of BMN 111 in children with ACH. Additional endpoints will also be examined. Secondary endpoints to determine the effects of BMN 111 include evaluation of change from baseline in body proportions of the extremities by anthropometry, bone physiology (including changes in bone morphology, quality, and growth via X-rays and dual X-ray absorptiometry (DXA) of the extremities and spine). Other secondary endpoints assessing quality of life and daily function of study subjects include health-related quality of life (HRQoL) and functional independence assessments. These endpoints include administration of the Pediatric Quality of Life Inventory (PedsQL), Quality of Life in Short Stature Youth (QoLISSY), and Functional Independence Measure (WeeFIM) assessments. The Child Behavior Checklist (CBCL) will also be administered. Additional exploratory endpoints include polysomnography to evaluate sleep apnea, BMN 111 activity biomarkers, and genomic biomarkers. Subjects who are in the control arm of the study who have been receiving placebo may be eligible to receive active treatment after they have completed the treatment period of the study.

7.5 Summary of Overall Risks and Benefits

7.5.1 Summary of Risks from Nonclinical Studies

CBI [redacted]

CBI

7.5.2 Summary of Risks from Clinical Studies

7.5.2.1 Study 111-101

Based on review of the first-in-human Phase 1 study of BMN 111 in healthy adult volunteers, Study 111-101, BMN 111 administered SC daily was well tolerated with doses ranging from 0.5 µg/kg to 15 µg/kg. All AEs were of mild severity, and no SAEs were reported. The most common AE was mild, transient, self-limited orthostatic hypotension, of which the majority of cases were asymptomatic and observed only upon assumption of an upright posture following recumbence. No dose-limiting toxicities were identified outside of these CV findings.

7.5.2.2 Study 111-202

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated. In addition BMN 111 at 15 µg/kg was well tolerated for over 12 months with no new safety concerns identified.

Based on review of data from the Phase 2 clinical trial, injection site reactions and hypotension have been identified as risks associated with BMN 111 injections. Hypersensitivity reactions including development of BMN 111 antibodies are potential risks associated with BMN 111 injections. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

7.5.3 Summary of Potential Benefits from Clinical Studies

For children with ACH who will receive BMN 111 as part of Study 111-301, potential benefits may include improvement of AGV rates such that their increase in growth velocity may approach that of children of average stature. Additional potential benefits may include improvement of the disproportionate growth as well as improvement in quality of life, activities of daily living, and medical complications of ACH. For example, improvement in height could have an impact on daily activity performance.

8 STUDY OBJECTIVES

The primary objective of the study is to:

- Evaluate change from baseline in annualized growth velocity at 52 weeks in subjects treated with BMN 111 compared with control subjects in the placebo group.

The secondary objectives of the study are to:

- Evaluate change from baseline in height Z-score in subjects treated with BMN 111 compared with control subjects in the placebo group at 52 weeks.
- Evaluate change from baseline in upper:lower segment body ratio in subjects treated with BMN 111 compared with control subjects in the placebo group at 52 weeks.
- Evaluate change from baseline in body proportion ratios of the extremities.
- Evaluate effect of BMN 111 on bone morphology/quality by X-ray and DXA.
- Evaluate potential changes in HRQoL as measured by the QoLISSY and PedsQL questionnaires.
- Evaluate potential changes in functional independence as measured by the WeeFIM clinician-reported outcome.
- Evaluate safety and tolerability of BMN 111 in children with ACH.
- Evaluate the pharmacokinetics of BMN 111.
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures.
- Evaluate change from baseline in bone metabolism biomarkers.

The exploratory objectives of the study are to:

- Evaluate sleep study scores by polysomnography in a subset of subjects.
- Evaluate biomarkers of BMN 111 activity.
- Evaluate genomic biomarkers.

9 INVESTIGATIONAL PLAN

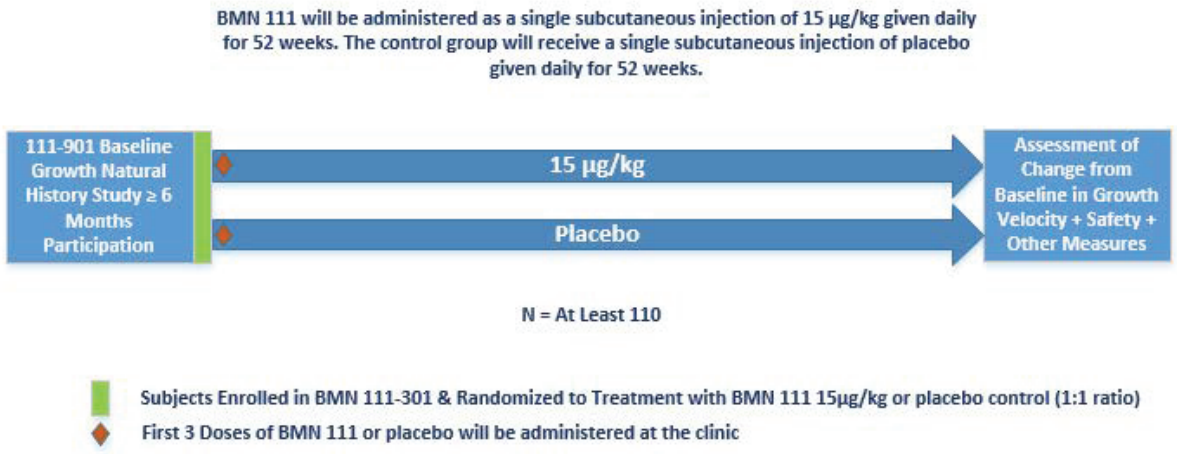
9.1 Overall Study Design and Plan

This is a Phase 3 randomized, placebo-controlled, double-blind multicenter study to evaluate the effect of BMN 111 on growth in children with ACH. Subjects who are 5 to < 18 years old with documented ACH confirmed by genetic testing will have been enrolled in Study 111-901 for at least a 6-month period immediately before study entry, and meet all study eligibility criteria will participate. At least 110 eligible subjects will be stratified based on sex and Tanner Stage (Stage 1, and > Stage 1) (with no greater than 20% of subjects > Tanner Stage 1), and randomly assigned in a 1:1 ratio to one of two treatment groups: placebo or BMN 111 at 15 µg/kg. To achieve gender balance, approximately 50% of each gender will be enrolled, with neither to exceed 55%. In Japan, subject enrollment will be staggered initially, with a minimum of a 2-week window between the first 4 subjects enrolled.

For placebo and BMN 111, the route of administration is subcutaneous injection and the frequency is daily. Approximately 33 clinical centers worldwide will participate in the study.

The 111-301 study design is presented below in Figure 9.1.1.

Figure 9.1.1: 111-301 Study Design



BMN 111 or placebo will be administered as a single subcutaneous dose of 15 µg/kg given daily for 52 weeks. The control group will receive subcutaneous injections with placebo daily for 52 weeks.

Safety monitoring will be conducted for all subjects randomized to BMN 111 or placebo after the first dose is received and over the duration of the study. This will include a minimum of 2 hours post-dose observation on the first 3 days of dosing and 30 minutes on all

other days of dose administration, in conjunction with caregiver training for BMN 111 or placebo administration and AE documentation/reporting. It is generally expected that after subjects are tolerating BMN 111 or placebo well and specified criteria have been met, caregivers will begin administering BMN 111 or placebo. If the caregiver is unable or unavailable to administer BMN 111 or placebo, home health care may be provided. Contact by a study staff member to the caregiver will be required every 4 weeks (± 10 days) to all study subjects after the Week 6 visit when there are no study visits or contact in the preceding 4 weeks. During these contacts, study staff will ask the caregiver about dose administration and seek information on adverse events (AEs) and serious AEs (SAEs) by specific questioning. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE electronic case report form (eCRF).

After the study is completed, subjects in both treatment and control groups will be eligible to receive BMN 111 in 111-302, to assess safety and efficacy of BMN 111 over the longer term. Subjects will have the option to enroll in 111-302 after the Week 52/Study Completion Visit. Week 52 assessments will serve as Baseline assessments for entry to study 111-302 if the visit occurs on the same day or within 2 weeks. Subjects who enroll into 111-302 more than 2 weeks after the 111-301 Week 52 visit will have a separate Baseline visit; the same assessments as those performed at Week 52 will be repeated at that time.

Data Monitoring Committee

In addition to safety monitoring by BioMarin personnel, an independent data monitoring committee (DMC) will act as an advisory body to BioMarin and provide input on the safety data collected in the study. DMC data review will occur at regular time periods during the study (or ad hoc, if indicated). Membership, roles, and responsibilities of the DMC will be outlined in a separate DMC charter.

Assessments

For a discussion of efficacy assessments, see Section 9.12.2, 9.12.3, and 9.12.4; exploratory assessments, Section 9.12.4; safety assessments, Section 9.12.6; and PK variables, Section 9.12.5.

A summary of events and assessments are provided by visit in Table 9.1.1.

Table 9.1.1: Schedule of Events for Subjects Randomized to Daily Investigational BMN 111 or Placebo Injections

Procedure	Screening Day -30 to Day -1[b]	Day 1	Day 2	Day 3	Day 10 ± 1 Day[a]	Week 6 ±7 Days	Week 13 ± 7 Days	Week 26 ± 7 Days	Week 39 ± 7 Days	Week 52 ± 7 Days	Safety Follow-up Week 56 ±7 Days[dd]	Early Term
Informed consent	X											
Medical history[c]	X											
Parental height[d]	X											
Diagnostic genetic testing (if needed)[e]	X											
Physical examination[f]	X	X			X	X	X	X	X	X	X	X
Tanner Stage of Pubertal Development	X							X		X		X
Menstrual history in female subjects (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[g]	X	X				X	X	X	X	X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X
Anthropometric measurements[i]	X	X					X	X	X	X		X[i]
Weight	X	X		X	X	X	X	X	X	X		X
HRQoL (PedsQL, QoLISSY), WeeFIM, and CBCL[j]	X							X		X		
Hip imaging via pelvis X-ray (AP view)	X											
Hip clinical assessment[k]	X							X		X		X
Sleep sub-study (optional)[l]	X[l]									X[l]		X[l]
ECG[m]	X	X			X		X	X	X	X	X	X
Echocardiogram	X											

Procedure	Screening Day -30 to Day -1[b]	Day 1	Day 2	Day 3	Day 10 ± 1 Day[a]	Week 6 ±7 Days	Week 13 ± 7 Days	Week 26 ± 7 Days	Week 39 ± 7 Days	Week 52 ± 7 Days	Safety Follow-up Week 56 ±7 Days[dd]	Early Term
Clinical labs (hematology, chemistry, and urinalysis)[n]	X	X			X	X	X	X	X	X	X	X
Thyroid function tests	X									X		X
Vitamin D, 25-hydroxy	X							X		X		X
Salivary cortisol	X							X		X		X
Serum prolactin	X							X		X		X
FSH/LH[o]	X							X		X		X
Anti-BMN 111 immunogenicity[p]		X					X	X	X	X	X	X
Bone metabolism blood biomarkers[q]		X					X	X	X	X	X	X
Bone metabolism urine biomarkers[r]		X					X	X	X	X	X	X
BMN 111 activity urine biomarkers (cGMP)[s]		X	X	X		X		X		X		
Urine chemistry[s]		X	X	X		X		X		X		
Genomic biomarkers (optional)						X				X		
PK[t]		X (full)					X (partial)	X (full)	X (partial)	X (full)		
DXA (BMD and BMC of whole body less head, spine)[u]	X							X		X		X[u]
Left hand and wrist X-ray (PA view)[v]	X							X		X		X[v]

Procedure	Screening Day -30 to Day -1[b]	Day 1	Day 2	Day 3	Day 10 ± 1 Day[a]	Week 6 ±7 Days	Week 13 ± 7 Days	Week 26 ± 7 Days	Week 39 ± 7 Days	Week 52 ± 7 Days	Safety Follow-up Week 56 ±7 Days[dd]	Early Term
Bilateral lower extremity X-rays including AP and lateral views[v]	X							X		X (Bilateral whole leg, AP only)		X[w]
Lumbar spine X-rays (AP and lateral views)[w]	X									X		X[w]
Injection site photos (optional)[x]		X						X		X		X[x]
Concomitant medications[y]	X	X	X	X	X	X	X	X	X	X	X	X
BMN 111 or placebo administration[z]		X	X	X	X	X	X	X	X	X		
BMN 111 or placebo accountability		X	X	X	X	X	X	X	X	X		X
Adverse events[aa]	X	X	X	X	X	X	X	X	X	X	X	X
Capture procedures/ interventions/surgeries[bb]		X	X	X	X	X	X	X	X	X	X	X
Contact for Study Follow Up[cc]	Required every 4 weeks (± 10 days) after the Week 6 visit when there are no study visits or contact in the preceding 4 weeks[dd]											

NOTE: ALL BLOOD AND URINE LABORATORY ASSESSMENTS ARE PRE-DOSE EXCEPT WHEN SPECIFIED. OTHER ASSESSMENTS CAN BE CONDUCTED EITHER PRE-DOSE OR POST-DOSE UNLESS OTHERWISE SPECIFIED.

a. Day 10 visit has a ± 1-day window; all subsequent visits have a ±7-day window.

b. If both visits are on the same day, the 111-901 procedures that can be used as the 111-301 screening data are outlined in the Study Reference Manual.

c. Demographics, medical history, including ACH-related history, should include all major illnesses, diagnoses, and surgeries that the subject has ever had; including any prior or existing medical conditions that might interfere with study participation or safety.

d. Standing height of the subject's biological parents may be assessed (optional) via height measurement or stated height. Height measurement can be done at any point in the study. Prior to the measurement being taken, each parent is required to complete an ICF specific to parent height assessment. The ICF will be signed prior to the assessment, which can be done at any point in the study. If the biological parent is not available during the course of the study to take his/her standing height, if consented, the biological parent can provide his/her stated height.

e. If subjects had previous genetic testing, subjects must have either a written letter by the physician confirming genetic testing, including the specific mutation required for Study 111-301 include the identification of FGFR3 mutation (G346E, G375C, G380R, or "other") OR a lab report from a certified laboratory with the study specific mutation documented.

f. Complete physical exam includes all major body systems.

g. Pregnancy test will be conducted at each indicated visit for female subjects who have begun menses or are 10 years of age and older. Either urine or serum test may be used. Serum pregnancy tests will be performed in the event that urine pregnancy test results are positive or equivocal (indeterminate).

h. All treatment visits have pre- and post-dose vital sign assessments. Left brachial arm should be the first method of assessment considered, and the same site should be used for blood pressure measurement in each subject throughout the study.

- **Pre-Dose vital sign assessments:** Vital signs at pre-dose include: body temperature in degrees Celsius (°C), heart rate, BP, and respiratory rate
    - Pre-dose vital signs should always be taken and recorded prior to pre-dose blood draw.
- **Post-dose vital sign assessments: Vital signs at post dose include heart rate and BP**
    - Vital signs should be taken prior to blood draws.
    - When blood samples and BP assessments are scheduled at the same time or within the same time window, BP should be measured before blood samples are drawn.
    - If a BP measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and at least 5 minutes before measuring BP.
    - Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
- **Hypotensive Event:**
- If a subject has symptoms potentially consistent with hypotension or a decrease in systolic BP of 20 mm Hg or more from pre-dose systolic BP, blood pressure and heart rate (BP/HR) should be measured and recorded approximately every 15 minutes for the first hour and every 30 minutes thereafter until the systolic BP returns to pre-dose systolic BP (or within the normal range for this subject as defined by PI) and symptoms (if present) resolve.

NOTE: If the hypotension resolves within the first hour and returns to the normal range, additional BP monitoring as described above is not required. Detailed guidance for blood pressure assessments is provided in the most recent Blood Pressure Instrument and Technique Guidelines.

Vital Sign Assessment Frequency		
Screening	After at least 5 min of rest, subject's BP is taken in sitting position. Then the subject will stand and BP will be taken again at approximately 1 and 3 minutes after standing.	
All other visits	After at least 5 min of rest, subject's BP is taken 1 time in sitting position.	
Assessment Frequency post- dose		
Dosing Visits	0-1 hr post-dose	1-2 hr post-dose
Days 1 Day 2 -3	Q15 min (± 5 min) Q30 min (± 5 min)	Q 30 min (± 5 min) Q30 min (± 5 min)
All other dosing visits: vital sign measurements are taken once per time point in a sitting position after at least 5 minutes of rest.	Q30 min (± 5 min); for 1 hour	

Note: Please reference the Blood Pressure Instrument and Technique Guidelines document for additional information on blood pressure measurement requirements.

i. Growth measures should be collected at approximately the same time each visit (± 2 hr from the time when the first measurement assessment was taken at Screening) by a study staff member, preferably the same person throughout the study, who has been trained by a BioMarin representative. Anthropometric measurements may include but are not limited to standing height; sitting height; weight; head circumference; upper and lower arm length; leg length; and arm span (See Anthropometric Measurement Guidelines). Anthropometric measurements will be taken three times in a row with the exception of weight, which is taken once. Anthropometric measurements will be taken at the early termination visit only if subject discontinues after Week 6 and > 2 weeks since previous anthropometric measurement assessment.

j. Reference the study-specific HRQoL and WeeFIM guidance documents. NOTE: for the Child Behavior Checklist (CBCL), no data will be collected from the language scale, as it is supplemental and not required to calculate any of the behavior measures.

k. Hip clinical assessment: this assessment will include medical history of the hip and physical exam (including observation of gait when possible) to determine changes in hip function or pain with hip (active and passive range of motion, when possible). Changes from baseline may trigger further evaluation based on the investigator's clinical assessment.

l. If sleep study results in a poor recording or is uninterpretable, the subject may need to repeat the assessment. Sleep study occurs at the early termination visit only if early termination visit occurs after Week 26 and subject has had a previous sleep study during the trial, ie, has entered the substudy.

m. A standard 12 lead ECG will include heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. All ECGs will be performed in triplicate at the visits indicated in the Schedule of Events (Table 9.1.1). ECGs will be performed post-dose on study day visits at which a dose is given; in addition, on Day 1, ECGs will be performed pre-dose. On days when PK samples are being drawn, ECGs should be performed within a 5-minute window prior to 30-minute PK assessment

n. Clinical labs (hematology, chemistry, and urinalysis) are all pre-dose collections.

o. FSH/LH will be monitored for all subjects >8 years of age, and for subjects at Tanner stage 2 (whichever is earlier).

p. Immunogenicity: Total and neutralizing anti-BMN 111 antibody samples (serum) will be drawn pre-dose on Day 1, Weeks 13, 26, 39, 52, and Safety Follow-Up or Early Termination visit as listed in the SOE. NAb testing and TAb testing for cross-reactivity with endogenous CNP, ANP or BNP will be performed only on Baseline and TAb positive samples. Blood (serum) samples for testing Total immunoglobulin E (IgE) and drug-specific IgE will be drawn on Day 1 and in the event of a Grade 3 or significant hypersensitivity adverse event, or at investigator or Sponsor discretion. The drug-specific IgE sample should be drawn at least 8 hr after the event start time or before the next dose. A sample for total IgE and serum tryptase should be drawn within 1 hour of the start of the event when possible or during the unscheduled safety visit.

q. Bone metabolism blood biomarker samples will be collected pre-dose on the indicated visits.

r. Bone metabolism urine biomarker samples will be collected as soon as possible upon arrival at the clinic. Each sample will be tested for biomarker concentration and creatinine concentration for normalization.

s. BMN 111 activity urine biomarker and urine chemistry samples will be collected pre-dose, and 1, 2, and 4 hr post-dose on the indicated visits (± 20 minutes for all urine sample time points). Each collection will be tested for biomarker concentration and urine creatinine concentration for normalization.

t. Full PK samples are collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45(± 5 min), 60 (± 5 min), 90 (± 5 min), 120 (± 5 min) minutes post dose at Day 1, Week 26, and Week 52 visits. Partial PK samples are collected pre-dose and at 15 (± 2 min), 30 (± 5 min), and 60 (± 5 min) minutes post-dose at Week 13 and Week 39 visits.

u. DXA at early termination visit only if subject discontinues after 9 months to reduce unnecessary radiation exposure (unless additional X-rays are recommended by investigator, BioMarin, or DMC).

v. Left hand and wrist X-ray (PA view), and bilateral X-ray of lower extremity (AP/lateral views) including distal femoral growth plate and proximal tibia growth plate. Week 52 X-ray is bilateral whole leg, AP only. X-rays are obtained at the early termination visit only if subject discontinues after 9 months to reduce unnecessary radiation exposure (unless additional procedure is recommended by investigator, BioMarin, or DMC). For PA of hand and wrist X-ray, the left-sided extremities should be first sites of assessment considered, and the same sites should be used for measurement in each subject throughout the study.

w. Lateral and AP lumbar spine X-rays at early termination visit only if subject discontinues after 9 months to reduce unnecessary radiation exposure (unless additional X-rays are recommended by investigator, BioMarin, or DMC).

x. Injection site photos are optional, but sites are strongly encouraged to take photos on Day 1, Week 26, Week 52, and Early Term Visit. During a scheduled visit, photos of the injection site will be taken in either of these two situations: 1) If an injection site reaction (ISR) occurs, photos will be taken for each ISR when it becomes apparent (or at onset), at most severe, and then post resolution. The time of the post-resolution photo may not be the same as the time the AE resolved, and this is expected. If the visit has ended and the ISR has not resolved, the subject is not expected to remain on site until ISR resolves. If the ISR is ongoing at the end of the visit, record as an ongoing AE. 2) If the subject has not had an ISR by the end of the study visit, a photo will still be taken of the injection site used on that day. In between visits, if an ISR worsens or changes in pattern, then the subject should have an unscheduled site visit. During the visit photos of the injection site with the ISR should be taken. Also, injection sites may be photographed if there is a new ISR or at any other time at the discretion/medical judgment of the investigator or as recommended by the sponsor.

y. All medications (prescription, over-the-counter and herbal) and nutritional supplements taken 30 days prior to Screening and throughout the study should be documented.

z. The same injection site should not be used 2 days in a row, and should be rotated between the four injection sites bilaterally (upper thigh, upper back of arm, abdomen or buttocks).

[aa.] After written informed consent but before study treatment initiation, only SAEs associated with protocol-imposed interventions will be recorded. After study drug initiation, all AEs and SAEs will be recorded until 4 weeks after either the last administration of study drug or the Early Termination visit. In the event of pregnancy the reporting period will be 12 weeks after either the last administration of study drug or the Early Termination visit. If a subject is discontinued from the study prematurely, AEs and SAEs will be recorded at the Early Termination visit.

[bb.] All procedures/interventions/surgeries will be recorded after informed consent is obtained and after the first administration of study drug, until 4 weeks after either the last administration of study drug or the Early Termination visit. If a subject is discontinued from the study prematurely, all procedures/interventions/surgeries will be recorded at the Early Termination visit.

[cc.] Contact by a study staff member to the caregiver will be required after the Week 6 visit every 4 weeks (±10 days) when there are no study visits or contact in the preceding 4 weeks. During these contacts, study staff will ask about dose administration and seek information on AEs and SAEs by specific questioning. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

[dd.] The 4-week safety follow up visit will be waived for subjects who enter BMN 111 study 111-302 within the 2-week period following last dose of study drug. If sponsor discontinues development program at any time, a 4-week safety follow-up visit should occur.

9.2 Discussion of Study Design, Including Choice of Control Group

The intent and design of this Phase 3 study is to assess BMN 111 as a therapeutic option for the treatment of children with ACH. The age range of enrollment of children with ACH has been chosen to be 5 to < 18 years old for this study. Identification of efficacy at this age range is congruent with mechanism of action of BMN 111, because BMN 111 is expected to act at open epiphyseal growth plates. Therefore, to have a potential therapeutic benefit for subjects with ACH, treatment is expected to be required prior to epiphyseal growth plate closure. The exact chronological age at which growth plates completely fuse is variable but is thought to occur sometime in late adolescence, hence the upper limit of the age range for subjects to be enrolled in this study is < 18 years old.

To achieve gender balance, approximately 50% of each gender will be enrolled, with neither to exceed 55%.

In terms of the study design, a randomized double-blind placebo control will be used to mitigate the risk of selection bias and any potential bias in data collection and study conduct. Additionally, this design provides a framework for interpretation of any endpoints with a subjective component, eg, HRQoL and functional independence questionnaires and any subjective assessment of safety.

9.3 Selection of Study Population

Subjects 5 to < 18 years old who have documented ACH, as documented by clinical grounds and confirmed by genetic testing, were selected to participate in this study. Additional criteria for participation in the study are provided in Sections 9.3.1and 9.3.2.

9.3.1 Inclusion Criteria

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

1. Parent(s) or guardian(s) are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, subjects under the age of majority are willing and able to provide written assent (if required by local regulations or the IRB/IEC/REB) after the nature of the study has been explained and prior to performance of any research-related procedure. Subjects who reach the age of majority while the study is ongoing will be asked to provide their own written consent.
2. 5 to < 18 years old at study entry.
3. Have ACH, documented by clinical grounds and confirmed by genetic testing.
4. Have at least a 6-month period of pretreatment growth assessments, including standing height, and are currently active participants in 111-901.
5. Females ≥ 10 years old or who have begun menses must have a negative pregnancy test at the Screening Visit and be willing to have additional pregnancy tests during the study.
6. If sexually active, willing to use contraception as specified in Section 9.3.3.
7. Are ambulatory and able to stand without assistance.
8. Are willing and able to perform all study procedures.
9. Caregivers are willing to administer daily injections to the subjects and complete the required training.

9.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

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

3. Have a history of any of the following:
    - Renal insufficiency defined as serum creatinine > 2 mg/dl.
    - Chronic anemia.
    - Baseline systolic blood pressure (BP) < 70 millimeters of mercury (mm Hg) or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms ie, dizziness, fainting) or recurrent symptomatic orthostatic hypotension.
    - Cardiac or vascular disease, including the following:
        - Cardiac dysfunction (abnormal echocardiogram [ECHO] including abnormal left ventricle [LV] mass) at Screening Visit.
        - Hypertrophic cardiomyopathy.
        - Pulmonary hypertension.
        - Congenital heart disease.
        - Cerebrovascular disease.
        - Aortic insufficiency or other clinically significant valvular dysfunction.
        - Clinically significant atrial or ventricular arrhythmias.
4. Have a clinically significant finding or arrhythmia on screening electrocardiogram (ECG) that indicates abnormal cardiac function or conduction or Fridericias corrected QT interval (QTc-F) > 450 msec.
5. Have an unstable condition likely to require surgical intervention during the study (including progressive cervical medullary compression or severe untreated sleep apnea).
6. Evidence of decreased growth velocity (AGV < 1.5 cm/year) as assessed over a period of at least 6 months or of growth plate closure (proximal tibia, distal femur) through bilateral lower extremity X-rays including both AP and lateral views.
7. Documented Vitamin D deficiency (concentration of blood 25-hydroxy-vitamin D < 12 ng/mL or < 30 nmol/L).
8. Require any investigational agent prior to completion of study period.
9. Have received another investigational product or investigational medical device within 6 months before the Screening Visit.
10. Have used any other investigational product or investigational medical device for the treatment of ACH or short stature at any time, including BMN 111.

11. Current chronic therapy with antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, GnRH agonists, any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function (Table 9.3.2.1).
12. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the previous 6 months or treatment greater than 6 months at any time.
13. Have had > 1 month treatment with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the previous 12 months.
14. Planned or expected to have limb-lengthening surgery during the study period. Subjects with previous limb-lengthening surgery may enroll if surgery occurred at least 18 months prior to screening and healing is complete without sequelae.
15. Planned or expected bone-related surgery (ie. surgery involving disruption of bone cortex, excluding tooth extraction), during the study period. Subjects with previous bone-related surgery may enroll if surgery occurred at least 6 months prior to screening and healing is complete without sequelae.
16. Have had a fracture of the long bones or spine within 6 months prior to screening.
17. Pregnant or breastfeeding at the Screening Visit or planning to become pregnant (self or partner) at any time during the study.
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at least 3 × upper limits of normal (ULN) or total bilirubin at least 2 × ULN (except for subjects with known history of Gilbert's disease).
19. History of severe untreated sleep apnea.
20. Have had new initiation of sleep apnea treatment (eg, continuous positive airway pressure [CPAP] or sleep apnea-mitigating surgery) in the previous 2 months prior to screening.
21. Have current malignancy, history of malignancy, or currently under work-up for suspected malignancy.
22. Have known hypersensitivity to BMN 111 or its excipients.
23. Have a history of hip surgery or hip dysplasia atypical for achondroplastic subjects.
24. Have clinically significant hip injury in the 30 days prior to screening.
25. History of slipped capital femoral epiphysis or avascular necrosis of the femoral head.

26. Are unable to lie flat when in prone position (needed for hip exam).
27. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the investigator.
28. Concurrent disease or condition that, in the view of the investigator, would interfere with study participation or safety evaluations, for any reason.
29. Have a condition or circumstance that, in the view of the investigator, places the subject at high risk for poor treatment compliance or for not completing the study.

Table 9.3.2.1: Current Chronic Therapy with Restricted Medications

Restricted Medications
• Antihypertensive medications • Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin II receptor blockers • Diuretics • Beta-blockers • Calcium-channel blockers • Cardiac glycosides • Systemic anticholinergic agents • GnRH agonists • Any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function • Any medication that in the investigator's judgment, may compromise the safety or ability of the subject to participate in the clinical trial

9.3.3 Use of Birth Control During and After Study Participation

Female subjects who choose to be sexually active must agree to use a highly effective method of birth control during the study and for 30 days after taking the last dose of study drug. This includes combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); intrauterine device (IUD); or intrauterine hormone-releasing systems.

Male subjects must use a double-barrier method of contraception during the study and for 3 months after taking the last dose of study drug. This includes a combination of male condom with either cap, diaphragm, or sponge with spermicide, which is considered an acceptable but not highly effective method. True abstinence from having heterosexual intercourse during the entire period of risk associated with study treatments can be used as an acceptable method of contraception if considered preferred and usual lifestyle of the participant. Periodic

abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of period at risk, and withdrawal are not acceptable methods of contraception.

9.3.4 Removal of Subjects from Treatment or Assessment

Subjects (or their legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out. BioMarin must be notified of all subject withdrawals as soon as possible.

Investigators may discontinue administration of BMN 111 or placebo at any time. Reasons for which the investigator or BioMarin will withdraw a subject from study treatment include, but are not limited to, the following:

1. Evidence of both (1) growth plate fusion as assessed by radiographic imaging of distal femur and proximal tibial and (2) decreased AGV (AGV < 1.5 cm/yr) as assessed over a period of at least 6 months. In case of discordant imaging and AGV, subject continuation will be discussed with BioMarin Medical Monitor, Principal Investigator and the DMC.
2. Subject experiences a serious or intolerable AE due to BMN 111 as determined by the investigator or sponsor.
3. Subject requires medication or medical procedure prohibited by the protocol.
4. Subject does not adhere to study requirements specified in the protocol.
5. Subject is lost to follow-up.
6. Subject becomes pregnant (refer to Section 10.3.1.11 for details on the reporting procedures to follow in the event of pregnancy).

If a subject fails to return for scheduled visits, documented effort must be made to determine the reason. If the subject's caregiver cannot be reached by telephone, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting that he or she contact the investigator. A copy of this letter and any response should be kept in the subject study records. If the subject cannot be contacted or does not respond, the subject will be considered lost to follow-up.

The investigator (or designee) must explain to each subject before enrollment into the study that the subject's protected health information obtained during the study may be shared with

BioMarin, regulatory agencies, and the IRB/IEC/REB. It is the investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) in the USA, from each subject (or the subject's legally authorized representative). If permission to use protected health information is withdrawn by the subject, it is the responsibility of the investigator to obtain a written request from the subject to ensure that no further data will be collected from the subject. The subject will then be removed from the study.

It is a priority of the study to maximize study subject retention and adherence to study-specific procedures. The completeness of the study data may affect the integrity and accuracy of the study results. Therefore, subjects who discontinue study treatment should be encouraged to continue to undergo as many of the protocol-specified procedures and assessments as possible for the remainder of the study, as long as such continued participation does not detrimentally affect the health, safety, or welfare of the subject and consent remains in place. It is important that following treatment discontinuation the original visit schedule is strictly adhered to.

For subjects who discontinue BMN 111 or placebo but remain in the study, PK and BMN 111 activity assessments will be waived completely; vital signs and clinical labs/biomarkers will be obtained only once at each visit subsequent to BMN 111 or placebo discontinuation. Pre-and post-dose designations will not apply as the subject has discontinued dosing and vital sign and clinical lab/biomarkers assessments previously designated as "post-dose" will be waived. All other assessments at each visit should be completed if possible and the subject is willing. Data from the study procedures and assessments may be used to further characterize the natural progression of ACH.

BioMarin reserves the right to discontinue the study at any time. Premature termination of the study may occur because of regulatory authority decision, a change in the opinion of the IRB/IEC/REB, clinical or safety reasons, or at the discretion of the Sponsor. The Sponsor reserves the right to discontinue the development of BMN 111 at any time, or to discontinue participation by an individual investigator or site for poor enrollment or noncompliance. Any decision to terminate the study will be promptly communicated to investigators, regulatory authorities, and IRB/IEC/REB. The investigator is responsible for communicating any decision to terminate a study to hospital staff involved in the conduct of the study and the participating subjects (and their families).

9.3.5 Subject Identification

Each subject will be assigned a unique subject identifier. This unique identifier will be on all eCRF pages.

9.3.6 Duration of Subject Participation

The planned duration of subject participation in this study is approximately 60 weeks, including up to 4 weeks of screening. After screening, subjects randomized to BMN 111 or placebo will receive study treatment daily for 52 weeks. Following completion of 52 weeks, subjects will be followed for safety for an additional 4 weeks. After the Phase 3 study has been completed, subjects in both the BMN 111 treatment arm and the control arm of the study may be eligible to receive BMN 111 over the longer term. If the sponsor discontinues development program at any time, a 4-week safety follow-up visit should occur.

Subjects who are not eligible to receive BMN 111 in a separate study will return at Week 56 for the Safety Follow-Up visit to assess for any AEs that may have occurred following completion of dosing.

Follow-up assessments and procedures should be performed as outlined in the Study 111-301 Schedule of Events (Table 9.1.1).

Subjects who discontinue from study treatment will be asked to complete study assessments and procedures for the remainder of the study. If subjects discontinue from study treatment and decline to participate for the remainder of the study, they will be asked to return for a final follow-up visit 4 weeks after their last study visit, and the agreement should be documented.

Subjects will participate in the study until completion or until one of the following occurs: the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the investigator or BioMarin (upon consultation and in agreement with the investigator) or the study is terminated.

9.4 Treatments

9.4.1 Treatments Administered

BioMarin and/or its designee will provide the study site with a supply of IP sufficient for the completion of the study.

Subjects will be randomized to BMN 111 at a daily dose of 15 µg/kg or placebo for the duration of the study. The normal dosing schedule is a single daily subcutaneous injection given 7 days a week.

If a recent acute illness associated with volume depletion (eg, nausea, vomiting, diarrhea) has not completely resolved prior to the first dose of BMN 111 or placebo, the dosing will be delayed until hydration status has improved (up to the maximum period allowed for the visit window).

9.4.1.1 BMN 111

During the study, BMN 111 will be administered as a single 15 µg/kg SC injection given daily at approximately the same time each day whenever possible. The same injection site should not be used 2 days in a row, and should be rotated between the four injection sites (upper thigh, upper back of arm, abdomen or buttocks). Doses may be administered in any of the common SC areas (upper arm, thigh, abdomen, buttocks). Following administration of each dose, subjects will be observed for at least 2 hours after the injection for Days 1 to 3, and 30 minutes for all other days of dose administration (longer if clinically indicated) either in the clinic by study personnel, by a home health nurse, or by a parent/caregiver. Instructions for home administration of BMN 111 for subjects who qualify for parent/caregiver administration are provided in the Study Drug Injection Guide and Injection media.

9.4.1.2 Placebo

During the study, placebo will be administered as a single SC injection given daily at approximately the same time each day whenever possible. The same injection site should not be used 2 days in a row, and should be rotated between the four injection sites (upper thigh, upper back of arm, abdomen or buttocks). Doses may be administered in any of the common SC areas (upper arm, thigh, abdomen, buttocks). Following administration of each dose, subjects will be observed for at least 2 hours after the injection for Days 1 to 3, and 30 minutes for all other days of dose administration (longer if clinically indicated) either in the clinic by study personnel, by a home health nurse, or by a parent/caregiver. Instructions for home administration of placebo for subjects who qualify for parent/caregiver administration are provided in the Study Drug Injection Guide and Injection media.

9.4.2 Identity of BMN 111

BMN 111 is cloned into the pJexpress401 vector, expressed in *E. coli* and then purified. The drug substance is a modified CNP peptide that retains wild-type activity and specificity. The modified CNP sequence is:

PGQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC

The amino acid sequence is an analogue of the naturally occurring tissue-expressed form of C-type natriuretic peptide (CNP-53). BMN 111 is a recombinant 39 amino acid peptide that includes the 37 C-terminal amino acids of the human CNP-53 sequence, and is engineered to include two additional amino acids (Pro-Gly) on the N-terminus, which renders the peptide more resistant to degradation. It is a cyclic peptide formed by an intramolecular disulfide bond. The molecular weight of the purified product is 4.1 kDa.

9.4.2.1 Product Characteristics and Labeling

The clinical drug product will be supplied in sterile, single-dose, Type I glass vials with coated stopper and flip-off aluminum cap. BMN 111 drug product is supplied as a 0.8-mg, or 2-mg lyophilized, preservative-free, white to yellow powder for reconstitution with commercially sourced sterile water for injection (WFI). The reconstituted solution is colorless to yellow and contains 0.8 mg/mL to 2 mg/ml of BMN 111, as well as citric acid, sodium citrate, trehalose, mannitol, methionine, polysorbate 80, and sterile WFI. The target pH of the reconstituted solution is 5.5. Sterile water for injection will be commercially sourced for reconstitution. All reconstitution and dose preparation steps should be performed as indicated in the Study Drug Injection Guide and Injection media.

BMN 111-placebo lyophilized product will be supplied in sterile, single-dose, Type I glass vials with coated stopper and flip-off aluminum cap. The placebo is designed to be comparable in appearance to the drug product and contains all of the components of the drug product including commercially sourced sterile WFI except the drug substance.

The BMN 111 or placebo kit label includes the following information: the contents, directions, lot number, quantity, subject ID, vial ID, investigator, the required storage conditions, a precautionary statement, the expiry date, the study number, and BioMarin Pharmaceutical name and location. This may vary based on country requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the Investigator's Brochure in a secure area accessible only to the designated pharmacists and clinical site personnel. All IP must be stored and inventoried and the inventories must be carefully and accurately documented according to applicable state, federal and local regulations, ICH good clinical practice (GCP), and study procedures.

Specific information for storage and return of BMN 111 or placebo is provided in the Pharmacy Manual, Study Drug Injection Guide, and Injection media.

9.4.4 Directions for Administration

Refer to the Study Drug Injection Guide for complete BMN 111 or placebo preparation instructions.

The injection will be administered as a daily dose of BMN 111 15 µg/kg or placebo given as a single subcutaneous injection. The dose should be given at approximately the same time every day whenever possible. Following administration of each dose, subjects will be observed for at least 2 hours after the injection for Days 1 to 3, and 30 minutes for all other dose administration days. Subjects should have adequate food intake prior to dosing. In the hour prior to injection, all subjects should have attempted to drink approximately 8-10 ounces or 240-300 mL of fluid (eg, water, milk, juice, etc).

Caregivers will administer BMN 111 or placebo at home once approved by the investigator and adequate training is demonstrated. Instructions on how to complete and document the training can be found in the Study Reference Manual. A caregiver will be eligible to administer BMN 111 or placebo if he or she meets all of the following criteria:

- The subject has been on a stable dosing regimen for a minimum of 3 days
- PI has approved administration of BMN 111 or placebo by the caregiver
- The caregiver has completed the Administration Training conducted by qualified study site personnel and has been observed by the study site personnel to be able to adequately prepare the proper dose and perform the injections safely

For dosing between planned clinic visits prior to caregiver approval, a home health nurse may administer BMN 111 or placebo, or subjects may be administered BMN 111 or placebo in the clinic by study staff or trained caregiver.

A subject's suitability for continued at-home drug administration will be evaluated by the investigator and the Sponsor's Medical Monitor if a subject experiences a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher AE that is considered possibly or probably drug-related, and/or a hypersensitivity reaction during the study.

Contact by a study staff member to the caregiver will be required after the Week 6 visit every 4 weeks (± 10 days) when there are no study visits or contact in the preceding 4 weeks. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

The investigator or the Sponsor's Medical Monitor may request that BMN 111 or placebo administration by the caregiver be halted at any time and that injections be administered by study site personnel or a home health nurse.

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 ratio, ie, injection with placebo: 15 µg/kg of BMN 111, using an interactive voice/web response system. The randomization will be based on Tanner Stage (Stage 1, or > Stage 1) and sex.

An independent third party vendor will develop the randomization schedule so that BioMarin and site personnel are blinded to treatment assignments.

9.4.6 Selection of Dose and Dosing Schedule Used in the Study

CBI

Thus to further confirm the potential improvement in growth using BMN 111 through a larger placebo-controlled Phase 3 study, the 15 µg/kg dose has been selected.

9.4.7 Blinding

An independent third-party vendor will develop the randomization schedule so that BioMarin and site personnel will not know treatment assignments. BMN 111 or placebo will be labeled with the study number and a unique identification number. Subjects and the participating site members will be blinded to the two study treatments (15 µg/kg BMN 111 or placebo).

The investigator and other members of site staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure. In the event of a medical emergency, the investigator may contact the Sponsor's Medical Monitor or other authorized BioMarin representative to discuss the necessity of unblinding the subject's treatment assignment. The blinded treatment assignments will be directly accessible to the investigator should a subject need to be unblinded in an emergency. If unblinding occurs, the investigator

or study pharmacist must record the reason for unblinding, as well as the date and time of the event. Corresponding information will be recorded on the eCRF by the investigator.

9.4.8 Prior and Concomitant Medications

All medications (prescription, over-the-counter and herbal), and nutritional supplements 30 days prior to screening and throughout the study will be recorded on the designated eCRF. The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the Sponsor's Medical Monitor must be notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study should be recorded on the eCRF. Concomitant medication information will be collected at the time points indicated in the Schedule of Events (Table 9.1.1). Restricted medications are listed in Table 9.3.2.1.

9.4.9 Treatment Compliance

Subjects will be instructed to return all used and unused BMN 111 or placebo kits at each study visit. Subject compliance with the dosing regimen will be assessed by reconciliation of the used and unused vials. The quantity dispensed, returned, used, lost, etc must be recorded on the dispensing log provided for the study.

The date, time, and volume of each dose of BMN 111 or placebo administered to each subject must be recorded. These data will be used to assess treatment compliance.

9.5 Investigational Product Accountability (BMN 111 or Placebo)

The investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, subjects to whom IP is dispensed (subject-by-subject kit specific accounting), and IP lost or accidentally or deliberately destroyed. The investigator or designee must retain all unused or expired study supplies until the study monitor (on-site CRA) has confirmed the accountability data.

9.5.1 Return and Disposition of Clinical Supplies

Unused BMN 111 or placebo must be kept in a secure location for accountability and reconciliation by the study monitor. The investigator or designee must provide an explanation for any destroyed or missing BMN 111 or placebo kits/vials.

Unused BMN 111 or placebo may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for destruction. The study monitor must account for all BMN 111 or placebo kits/vials in a formal reconciliation process prior to

destruction. The site must document all BMN 111 or placebo destroyed on site, and documentation must be provided to BioMarin and retained in the investigator study files. If a site is unable to destroy BMN 111 or placebo appropriately, the site can, upon request, return unused BMN 111 or placebo to the BioMarin contracted facility. The return of all BMN 111 or placebo kits/vials must also be documented and accounted for per instructions provided by BioMarin.

All BMN 111 or placebo and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

Caregivers of subjects who qualify for home administration of study BMN 111 or placebo will be provided with instructions for returning used and unused kits and the proper disposal of any ancillary supplies.

9.6 Dietary or Other Protocol Restrictions

BMN 111 will be administered as a single daily dose of 15 µg/kg SC injection given daily at approximately the same time each day whenever possible. Placebo will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Following administration of each dose, subjects will be observed for at least 2 hours after the injection for observation for Days 1 to 3, and 30 minutes for all other days of dose administration.

Subjects should have an adequate food intake. In the hour prior to injection, all subjects should have attempted to drink approximately 8-10 ounces or 240-300 mL of fluid (eg, water, milk, juice).

9.7 Demographic Data and Medical History

Demographic data and a detailed medical history will be obtained at Screening. This medical history should elicit 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.

9.8 Biological Parental Standing Height

Standing height of the subject's biological parents will be assessed via height measurement or stated height. Height measurement can be done at any point in the study. Prior to the measurement being taken, each parent is required to complete an ICF specific to parent height assessment. The ICF will be signed prior to the assessment, which can be done at any point in the study. If the biological parent is not available during the course of the study to

take his/her standing height, if consented, the biological parent can provide his/her stated height.

9.9 Physical Examination Findings

Physical examination will include assessment of general appearance; CV; dermatologic; head, eyes, ears, nose, and throat; lymphatic; respiratory; gastrointestinal (GI); musculoskeletal; and neurological/psychological and genitourinary. Other body systems may be examined. Screening results will be the baseline values and clinically significant changes from baseline will be recorded as an AE or SAE and study drug related or unrelated when appropriate based on the investigator's clinical judgment.

9.10 Tanner Stage of Pubertal Development

Tanner stage of Pubertal Development will also be assessed by the investigator (MD) or sub-investigator (MD) when indicated on the Schedule of Events (Table 9.1.1). The Tanner stage assessment document is included in the Study Reference Manual.

9.11 Echocardiogram

Cardiac anatomy and function will be evaluated by a standard 2-dimensional Doppler echocardiogram by a cardiologist. Echocardiograms will be performed at screening and provide information regarding cardiac anatomy and function prior to enrollment in the study.

9.12 Efficacy and Safety Variables

9.12.1 Efficacy and Safety Measurements Assessed

Table 9.1.1 describes the timing of required evaluations in subjects who are randomized to receive BMN 111 or placebo.

9.12.2 Primary Efficacy Variable

The primary efficacy endpoint is change from baseline in height growth velocity (annualized to cm/yr).

Growth measures may be collected approximately the same time each visit (± 2 hr from the time when the first measurement assessment was taken at Screening) by a study staff member, preferably the same person throughout the study, who has been trained by a BioMarin representative. Standardized measuring equipment and detailed measurement techniques are detailed in the Anthropometric Measurement Guidelines.

9.12.3 Secondary Efficacy Variables

Secondary efficacy endpoints include absolute height Z-score, upper:lower segment body ratio, body proportion ratios of the extremities, HRQoL (QoLISSY, PedsQL) questionnaires, and assessment of functional independence (WeeFIM).

Weight will be measured at Screening and at study visits as indicated on the Schedule of Events (Table 9.1.1). Standardized measuring equipment and detailed measurement techniques are detailed in the Anthropometric Measurement Guidelines

9.12.3.1 Height

Change from baseline in height will be evaluated using height Z-scores. Growth measures may be collected approximately the same time each visit (± 2 hr from the time when the first measurement assessment was taken at Screening) by a study staff member, preferably the same person throughout the study, who has been trained by a BioMarin representative.

9.12.3.2 Body Proportion Ratio of Upper to Lower Segment

Change from baseline in the ratio of the upper to lower body segments will be evaluated using anthropometric measurements and measurement ratios. Measurements not taken in the midsagittal plane should be taken on the right side of the body when possible.

Standardized measuring equipment and detailed measurement techniques are detailed in the Anthropometric Measurement Guidelines.

9.12.3.3 Body Proportion Ratios of the Extremities

Change from baseline in body proportion ratios of the extremities will be evaluated using anthropometric measurements and measurement ratios. Measurements not taken in the midsagittal plane should be taken on the right side of the body when possible.

Body proportion measurements of the extremities may include, but are not limited to, upper arm:forearm length ratio, upper leg:lower leg length ratio, and armspan:standing height ratio.

Standardized measuring equipment and detailed measurement techniques are detailed in the Anthropometric Measurement Guidelines.

9.12.3.4 Health-related Quality of Life and Functional Independence Measure

HRQoL questionnaires will be administered to assess the health-related quality of life of study subjects. The Functional independence measure (WeeFIM) will be used in study subjects to assess functional independence. HRQoL and functional independence will be assessed at the time points indicated in the Schedules of Events (Table 9.1.1). These

assessments will be implemented in those countries where country-specific versions are available.

9.12.3.4.1 Pediatric Quality of Life Inventory

The PedsQL measurement model was designed to measure health-related quality of life (QoL) in children and adolescents. It is a generic tool that includes measurement of physical, emotional, social, and school functioning, and has both child self-report and parent-report versions.

9.12.3.4.2 Quality of Life in Short Stature Youth

The QoLISSY questionnaire is a disease-specific patient-reported outcome (PRO) tool consisting of questions across seven domains (Physical QoL, Social QoL, Emotional QoL, Coping, Beliefs about Height, Future and Effects on Parents) and has both child self-report and parent-report versions.

9.12.3.4.3 Functional Independence Measure

The WeeFIM instrument is an assessment tool that measures functional performance across three domains (self-care, mobility and cognition) (Ireland, 2011; Ireland, 2012).

The WeeFIM instrument has been used in previous research in children with ACH, and has identified ongoing limitations in functional performance across these domains extending beyond the age of 7 years (Ireland, 2011). Because the WeeFIM considers the child's performance from a caregiver's perspective (Ireland, 2012), this tool in turn gives an indication of "burden of care" for families and caregivers of children with ACH.

9.12.4 Exploratory Efficacy Variables

9.12.4.1 Sleep Sub-Study

Given that sleep apnea is a finding in children with ACH (Waters, 1993,) and has implications on functional and health outcomes, an optional sleep sub-study will be performed in a limited number of qualified sleep centers for a subset of subjects. 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).

9.12.4.2 BMN 111 Activity Biomarkers

Biomarkers may include but are not limited to assessment of changes in bone and collagen metabolism and BMN 111 bioactivity. BioMarin or designee will perform analysis, and samples may also be used for assay development.

Samples for blood and/or urine biomarkers will be collected at the time points presented in the Schedule of Events (Table 9.1.1). Refer to the Study Laboratory Manual for instructions regarding obtaining and shipping samples. The sample type will also be included in the Study Laboratory Manual.

9.12.4.3 Biomarker Research Sample Analyses

All samples collected in this study may be used for exploratory biomarker research once the primary use has been completed.

For each portion of the blood and urine samples reserved for protocol-specified analyses, there may be multiple sample aliquots. Once samples have been successfully analyzed during the study, unused sample portions may be used during the study for assay development or other purposes stated in this section.

9.12.4.4 Genomic Biomarker Analysis

While the inherited FGFR3 mutations associated with achondroplasia are well characterized, disease phenotype in monogeneic diseases is often modified by variants in other genes. To identify and study genetic variants that may modify achondroplasia, a whole blood sample will be collected. Exploratory genomics will include, but are not limited to NPR-B, BRAF, and other genes associated with CNP signaling. Exploratory genomic analysis may inform understanding of the BMN 111 mechanism of action in achondroplasia. Exploratory genomics will not be conducted without express consent from the subject and his/her legally authorized representative (parent or legal guardian).

9.12.5 Pharmacokinetics Variables

Full PK samples are collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), 120 (± 5 min) minutes post dose at Day 1, Week 26, and Week 52 visits. Partial PK samples are collected pre-dose and at 15 (± 2 min), 30 (± 5 min), and 60 (± 5 min) minutes post dose at Week 13 and Week 39 visits.

Whenever possible, the following PK parameters for subjects randomized to the BMN 111 treatment group will be estimated by non-compartmental analysis:

- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$).

- Area under the plasma concentration-time curve from time 0 to the time of last measurable concentration (AUC_{0-t}).
- $C_{max.}$
- $T_{max.}$
- Elimination half-life ($t_{1/2}$).
- Apparent clearance (CL/F).
- Apparent volume of distribution (V_z/F).

Refer to the Study Laboratory Manual for additional instructions regarding obtaining and shipping samples. BioMarin will perform sample analysis, and samples may also be used for assay development.

9.12.6 Safety Variables

Safety will be evaluated by the incidence of AEs, SAEs, and clinically significant changes in vital signs, physical examination, ECG, X-ray/DXA assessments of bone morphology, quality, and growth of the extremities and spine (X-rays only), laboratory test results (urinalysis, chemistry, hematology), and CBCL assessments. Imaging (X-ray/DXA assessments), hip monitoring, biomarker, immunogenicity, salivary cortisol, serum prolactin, follicle stimulating (FSH)/luteinizing hormone (LH) levels, and physical measurement data will be utilized for safety-related reviews and analysis. FSH/LH will be monitored for all subjects > 8 years of age, and for subjects at Tanner stage 2 (whichever is earlier). Additional assessments will be conducted to evaluate changes from baseline in bone metabolism.

9.12.6.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject receives study drug. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in the Schedule of Events Table 9.1.1). Additionally, contact by a study staff member to the caregiver will be required approximately every 4 weeks (+/- 10 days) after the Week 6 visit when there are no study visits or contact within in the preceding 4 weeks. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

9.12.6.2 Procedures During the Study

All procedures/intervention/surgery will be recorded after informed consent is obtained and after the first administration of study drug, until 4 weeks after either the last administration of

study drug or the Early Termination visit. If a subject is discontinued from the study prematurely, all procedures/intervention/surgery will be recorded at the Early Termination visit.

9.12.6.3 Bone Morphology, Bone Mineral Density, Bone Mineral Content and Bone Age

The effect of BMN 111 on bone morphology and pathology will be assessed by X-ray and bone mineral density (BMD) and bone mineral content (BMC) by DXA. Bone growth and age will be assessed by the means of X-rays of wrist/hand.

9.12.6.4 Imaging Assessment Procedures (per Schedule of Events)

Imaging assessment procedures for all visits must be performed using the same instruments.

- Left hand and wrist X-ray, posterior-anterior (PA) view, to assess bone age (Greulich, 1971,; Tanner, 1975,).
- Bilateral X-rays of lower extremity (anterior-posterior [AP] and lateral views) to assess growth plates.
- Hip imaging via pelvis X-ray to identify hip pathology if clinically indicated by clinical hip assessment.
- Lumbar spine X-rays to measure changes from baseline in bone morphology and pathology.
- DXA scan (whole body less head, spine) to assess bone mineral density (BMD) and bone mineral content (BMC).

Additional imaging may be conducted should there be any issues or concerns with the subject's imaging assessments; one example is a situation in which the lower extremity X-rays are not sufficient to determine whether the subject's distal, femoral, and proximal tibia growth plates are closed. Imaging assessments will be collected and interpreted by a central reader. If clinically significant abnormalities are noted, the investigator or designee is required to assess whether it is appropriate to report an AE and if the subject should continue in the study. Refer to the vendor Imaging Guidelines for detailed imaging assessment requirements and procedures.

9.12.6.5 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in the Schedule of Events (Table 9.1.1). The scheduled clinical laboratory tests are listed in Table 9.12.6.5.1. Refer to the Study Laboratory Manual for instructions on obtaining and shipping samples.

Any test results may be repeated at the discretion of the investigator or sponsor.
The investigator should assess all test results, in addition to signing, dating, and including a comment on the laboratory report whether or not any abnormal result is clinically significant. Please refer to Section 10.3.1.6 for further guidance on reporting abnormal test results as an adverse event.

If there is an abnormal test result determined to be clinically significant by the investigator it should be repeated (at the investigator's discretion) until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the investigator determines that the abnormal value is no longer clinically significant.

Table 9.12.6.5.1: Clinical Laboratory Tests

Blood Chemistry	Hematology	Urinalysis
Albumin Alkaline phosphatase, total ALT (SGPT) AST (SGOT) Direct bilirubin Total bilirubin BUN Calcium Chloride Potassium Sodium Glucose	Hemoglobin Hematocrit WBC count RBC count Platelet count Differential cell count	Appearance Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Hemoglobin
Bicarbonate LDH Phosphorus Total protein 25-hydroxy Vitamin D Creatinine Thyroid function (TSH, FT4; if either TSH and FT4 are abnormal then T3 may be measured in addition)		Urine Chemistry Urine creatinine Urine sodium Urine potassium

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; cGMP, cyclic guanosine monophosphate; FT4, free thyroxine; LDH, lactate dehydrogenase; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; T3, triiodothyronine; TSH, thyroid stimulating hormone; WBC, white blood cell.

9.12.6.6 Other Laboratory Assessments

Subjects will be asked to provide blood and urine at the times indicated in the Schedule of Events (Table 9.1.1). Blood volume for testing has been reduced to the minimum necessary for adequate evaluation of efficacy and safety of BMN 111.

For subjects who have not previously had genetic testing confirming diagnosis of ACH, molecular genetic diagnosis to identify the FGFR3 mutation (G346E, G375C, G380R, or "other") will be performed. If subjects had previous genetic testing, subjects must have either a written letter by the physician confirming genetic testing, including the specific mutation, or a lab report from a certified laboratory with the study specific mutation documented.

Scheduled biomarker and anti-BMN 111 antibodies collections are listed in Table 9.12.6.6.1.

Table 9.12.6.6.1: Biomarkers and Anti-BMN 111 Antibodies

Blood Special Chemistry	Urine Biomarkers
Bone metabolism biomarkers	Bone metabolism urine biomarkers
Genomic biomarkers	BMN 111 pharmacodynamics biomarkers (cGMP)
Anti-BMN 111 antibodies	

9.12.6.7 Child Behavior Checklist

The CBCL 1.5 - 5 and the CBCL 6 - 18 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 should be used in children aged 5 to < 6 years old. The CBCL 6 - 18 years old should be used in children aged 6 up to 18 years old. No data will be collected from the language scale, as it is supplemental and not required to calculate any of the behavior measures.

The form requires approximately 15 minutes to complete. The checklist yields scores in the following areas: reactivity, anxiety, depression, somatic complaints, withdrawal, sleep problems, attention problems, and aggressive behavior.

The CBCL assessment will be implemented in those countries where country-specific versions are available.

9.12.6.8 Bone Metabolism Biomarkers

Bone metabolism biomarkers will be collected to assess changes in bone metabolism. BioMarin or designee will perform analysis, and samples may also be used for assay development.

Samples for bone metabolism biomarkers will be collected at the time points presented in the Schedule of Events (Table 9.1.1). Refer to the Study Laboratory Manual for instructions regarding obtaining and shipping samples. The sample type will also be included in the Study Laboratory Manual.

9.12.6.9 Vital Signs, Physical Examinations and Other Observations Related to Safety

9.12.6.9.1 Vital Signs

Vital signs assessed pre-dose will include seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). All treatment visits have pre-dose vital sign assessments. Post-dose measurements include heart rate and BP. For all dosing visits, assessment frequency is detailed in Table 9.12.6.9.1.1 (see Schedule of Events, Table 9.1.1).

At Screening, after at least 5 minutes of rest, subject's BP is taken in sitting position. Then the subject will stand and BP will be taken again at approximately 1 and 3 minutes after standing. At other visits, vital sign measurements are taken once per time point in a sitting position after at least 5 minutes of rest. Heart rate should be taken at each time point that BP is measured. When blood samples and BP assessments are scheduled at the same time or within the same time window, BP should be measured before blood samples are drawn. If a BP measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and wait several minutes before measuring BP. Pre-dose vital signs should always be taken and recorded prior to pre-dose blood draw. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.

If a subject has symptoms potentially consistent with hypotension or a decrease in SBP of 20 mm Hg or more from pre-dose SBP, blood pressure and heart rate (HR) should be measured and recorded approximately every 15 minutes for the first hour and every 30 minutes thereafter until the systolic BP returns to pre-dose systolic BP (or within the normal range for this subject as defined by PI) and symptoms (if present) resolve. If the hypotension resolves within the first hour and returns to the normal range, additional BP monitoring as described above is not required. Detailed guidance for blood pressure measurements is provided in the Blood Pressure Instrument and Technique Guidelines.

Table 9.12.6.9.1.1: Vital Sign Assessment Frequency

Vital Sign Assessment Frequency Pre-Dose		
Screening	After at least 5 min of rest, subject's BP is taken in sitting position. Then the subject will stand and BP will be taken again at approximately 1 and 3 minutes after standing.	
All other visits	After at least 5 min of rest, subject's BP is taken 1 time in sitting position	
Assessment Frequency Post-Dose		
Dosing Visits	0-1 hr post-dose	1-2 hr. post-dose
Days 1 Day 2 -3	Q15 min (± 5 min) Q30 min (± 5 min)	Q 30 min (± 5 min) Q30 min (± 5 min)
All other dosing visits: vital sign measurements are taken once per time point in a sitting position after at least 5 minutes of rest.	Q 30 min (± 5 min); for 1 hour	

9.12.6.10 Mitigating the Risk of Potential Hypotension

Study personnel and caregivers should be made aware of the potential risk of hypotension with BMN 111 administration. Subjects must be well hydrated and at a minimum eat a light snack prior to administration of BMN 111 or placebo. In the hour prior to injection, all subjects should have attempted to drink approximately 8-10 ounces or 240-300 mL of fluid (eg, water, milk, juice). If a recent acute illness associated with volume depletion (eg, nausea, vomiting, diarrhea) has not completely resolved prior to the first dose of BMN 111 or placebo, BMN 111 or placebo dosing may be delayed until hydration status has improved (up to the maximum period allowed for the screening window).

Caregivers should be trained to observe and recognize the symptoms of dehydration (eg, from fever, vomiting, diarrhea) and contact the investigator prior to BMN 111 or placebo administration if dehydration is suspected. Site personnel and caregivers should be trained to identify the symptoms of hypotension and, if they occur, should implement first-aid strategies at the discretion of the investigator such as having the subject lie down supine, elevating the lower extremities, and administering fluids. For guidelines on how to report adverse events associated with hypotension, refer to Section 10.

9.12.6.11 Electrocardiography

A standard 12-lead ECG will include heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. All ECGs will be performed in triplicate at the visits indicated in the Schedule of Events (Table 9.1.1). ECGs will be performed post-dose on study day visits at which a dose is given; in addition, on Day 1, ECGs will be performed pre-dose. On days when PK samples are being drawn, ECGs should be performed within a 5-minute window prior to 30-minute PK assessment.

9.12.6.12 Hip Clinical Assessment

The hip clinical assessment should be completed by an appropriately qualified health care professional at the time points indicated in the Schedule of Events (Table 9.1.1). Medical history will be obtained to evaluate for hip, thigh, or knee pain, or change in gait. The physical exam (including observation of gait when possible) identifies and evaluates any changes in hip function or pain with assessment of active and passive range of motion. Changes from baseline may trigger further evaluation based on the investigator's clinical assessment, which may include hip imaging and/or orthopedic consultation. If findings on clinical hip exam are determined to be clinically significant by the investigator and in consultation with Sponsor's Medical Monitor and orthopedic specialist (if needed), the DMC will be notified of AEs resulting from clinically significant abnormal hip monitoring assessments. DMC may provide recommendations as to if/when BMN 111 or placebo treatment should be temporarily or permanently discontinued.

9.12.6.13 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 (Table 9.1.1). Start date of menses will be captured. Female subjects with a positive pregnancy test at any time will be withdrawn from BMN 111 or placebo treatment.

Serum pregnancy tests will be performed in the event that urine pregnancy test results are positive or equivocal (indeterminate).

Refer to Section 10.3.1.11 for details on the reporting procedures to follow in the event of pregnancy.

9.12.6.14 Pediatric Blood Volume

Clinical labs and immunogenicity samples are necessary to perform to adequate safety assessment in this study. The objectives of testing pharmacodynamics biomarkers are to demonstrate biologic activity of BMN 111 and to understand the impact of immune responses on drug activity; and for exploratory blood biomarkers, to investigate the effects of treatment on changes in bone metabolism and endogenous CNP production.

To minimize blood collection volumes, assay technologies were chosen that are capable of sensitively detecting analytes using the lowest possible volume of blood for analysis. Additionally, assays capable of detecting analytes in urine rather than blood have been selected where possible. Blood volume for testing has been reduced to the minimum necessary for adequate evaluation of efficacy and safety of BMN 111.

9.12.6.15 Anti- BMN 111 Immunogenicity Assessments

Subjects randomized to receive BMN 111 or placebo will undergo immunogenicity testing. Blood (serum) samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 9.1.1) and testing performed using validated assays. Neutralizing antibody (NAb) testing will be performed on Baseline and TAb positive samples.

Scheduled samples will be tested in one or more of the following assessments:

- Anti- BMN 111 total antibody (TAb).
- Anti-BMN 111 antibody cross-reactivity with endogenous CNP, ANP, and BNP (TAb).
- Anti- BMN 111 Nab.

Testing for the presence of cross-reactive antibodies that bind to endogenous CNP, ANP, or BNP and for the presence of BMN 111 NAbs will be performed on baseline samples and anti- BMN 111 TAb-positive samples. Baseline NAb sample and cross-reactive TAb sample testing will be done at any time prior to the end of study.

9.12.6.16 Ad Hoc Safety Assessments

Samples for total immunoglobulin E (IgE) and drug-specific IgE testing will be drawn on Day 1 and in the event of a significant hypersensitivity AE, or at the discretion of the investigator and/or BioMarin. A significant hypersensitivity AE is defined as an event that is grade 3 or higher, requires temporary or permanent cessation of BMN 111, or is determined to be significant at the discretion of investigator and/or BioMarin (excluding reactions that are solely a localized injection site reaction). If a hypersensitivity AE occurs, an unscheduled safety visit should occur no later than 48 hours of the start of the reaction, including inspection of the injection site and clinical laboratory tests.

Blood (serum) samples should be collected and tested in one or more of the following assessments:

- Drug-specific IgE
- Total IgE
- Serum tryptase

If feasible, a sample for drug-specific IgE should be drawn no sooner than 8 hours after the event start time or before the next dose. A sample for total IgE and serum tryptase should also be drawn within 1 hour of the start of the event when possible or during the unscheduled safety visit.

A localized injection site reaction is defined as skin signs or symptoms restricted to one affected primary location, ie, hives, wheals, or swelling or an area of erythema, redness, induration, pain, or itching at or near the site of injection. Management of such localized reactions should be determined by the investigator's clinical judgment in consultation with the Sponsor's Medical Monitor (if warranted).

9.12.6.17 HPA Axis Assessments

To address potential effects of BMN 111 on activation of the hypothalamic pituitary adrenal (HPA) axis, assessment of salivary cortisol, serum prolactin levels, and FSH / LH will be analyzed at the time points indicated in the Schedule of Events (Table 9.1.1). FSH / LH will be done for all subjects > 8 years old or Tanner Stage 2 (whichever is earlier). These tests will be done at Baseline, Week 26, and Week 52.

9.12.6.18 Unscheduled Safety Visits

Unforeseen circumstances may arise in which an unscheduled visit may be needed. In such a case, the procedures performed at the unscheduled visit will be completed on a case-by-case basis.

9.12.6.19 Medical Photography

Injection site photos are optional, but sites are strongly encouraged to take photos on Day 1, Week 26, Week 52, and Early Termination visit. During a scheduled visit, if photos are being planned, photos of the injection site will be taken in either of these two situations: 1) If an injection site reaction (ISR) occurs, photos will be taken for each ISR when it becomes apparent (or at onset), at most severe, and then post resolution. The time of the post-resolution photo may not be the same as the time the AE resolved, and this is expected. If the visit has ended and the ISR has not resolved, the subject is not expected to remain on site until ISR resolves. If the ISR is ongoing at the end of the visit, record as an ongoing AE. 2) If the subject has not had an ISR by the end of the study visit, a photo will still be taken of the injection site used on that day. The site is instructed to document the absence of an ISR on the injection administration eCRF. In between visits, if an ISR worsens or changes in pattern, then the subject should have an unscheduled site visit. During the visit, photos of the injection site with the ISR may be taken. Also, injection sites may be photographed if there is a new ISR or at any other time at the discretion/medical judgment of the investigator or as recommended by the sponsor.

10 REPORTING ADVERSE EVENTS

10.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-defined events of special interest that are deemed critical to the safety evaluation of the study drug.

10.1.1 Adverse Events

For this protocol, a reportable AE is any untoward medical occurrence (eg, sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures, medication washout, or no-treatment run-in).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study-drug and the AE.

10.1.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose meets one or more of the following criteria:

- Is fatal.
- Is life threatening

  Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability or incapacity.

- Is a congenital anomaly or birth defect in the child or fetus of a subject exposed to IP prior to conception or during pregnancy.
- Is an important medical event or reaction – that, based on medical judgment, may jeopardize the subject or require intervention to prevent one of the above consequences (eg, anaphylaxis).

All adverse events that do not meet any of the criteria for SAEs should be regarded as non-serious AEs.

10.1.3 Events of Special Interest

The following events of special interest (EOSI) need to be reported to the Sponsor within 24 hours of site awareness, irrespective of seriousness, severity or causality:

- Fracture
- Slipped capital femoral epiphysis
- Avascular necrosis or osteonecrosis

10.2 Methods and Timing for Capturing and Assessing Safety Parameters

10.2.1 Adverse Event Reporting Period

The study AE reporting period is as follows: after informed consent but prior to initiation of study treatment, only SAEs associated with any protocol-imposed interventions will be reported. 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 (refer to Section 12.4). The criteria for determining, and the reporting of, SAEs is provided in Section 10.1.2.

10.2.2 Eliciting Adverse Events

Investigators will seek information on AEs and SAEs at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

10.2.3 Assessment of Seriousness, Severity, and Causality

The investigator responsible for the care of the subject or qualified medical designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.1.2 for SAE definitions). These assessments must be made by a study clinician with the training and authority to make a diagnosis (eg, MD/DO, physician's assistant, nurse practitioner, or DDS).

10.2.3.1 Seriousness

The investigator will assess if an AE should be classified as "serious" based on the seriousness criteria enumerated in Section 10.1.2. Seriousness serves as a guide for defining regulatory reporting obligations.

10.2.3.2 Severity

Severity (as in mild, moderate, or severe headache) is not equivalent to seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The severity of each will be assessed using the defined categories in Table 10.2.3.2.1.

The investigator will determine the severity of each AE and SAE [and EOSI, if applicable] using the National Cancer Institute (NCI) CTCAE v4. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4 as stated below.

Table 10.2.3.2.1: Adverse Event Grading (Severity) Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	
2	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]	
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]	
4	Life threatening consequences; urgent intervention indicated	**Grade 4 and 5 AEs should always be reported as SAEs**
5	Death related to AE	

[a] Instrumental ADL refers to the following examples: preparing meals, shopping for groceries or clothes, using the telephone, managing money.

[b] Self-care ADL refer to the following examples: bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden.

10.2.3.3 Causality

The investigator will determine the relationship of an AE to the study drug and will record it on the source documents and AE CRF. To ensure consistency of causality assessments, investigators should apply the guidance in Table 10.2.3.3.1.

Table 10.2.3.3.1: Causality Attribution Guidance

Relationship	Description
Not Related	• Exposure to the IP has not occurred OR • The administration of the IP and the occurrence of the AE are not reasonably related in time OR • The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IP.
Related	• The administration of the IP and the occurrence of the AE are reasonably related in time AND • The AE could possibly be explained by factors or causes other than exposure to the IP OR • The administration of IP and the occurrence of the AE are reasonably related in time AND • The AE is more likely explained by exposure to the IP than by other factors or causes.

Factors suggestive of a causal relationship could include (but are not limited to):

- Plausible temporal relationship.
- Absence of alternative explanations.
- Rarity of event in a given subject or disease state.
- Absence of event prior to study drug exposure.
- Consistency with study product pharmacology.
- Known relationship to underlying mechanism of study drug action.
- Similarity to adverse reactions seen with related drug products.
- Abatement of AE with discontinuation of study drug, and/or recurrence of AE with reintroduction of study drug.

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.3 Procedures for Recording Adverse Events

10.3.1 Recording Adverse Events on an eCRF

Investigators should use precise medical terminology when recording AEs or SAEs on an eCRF. Avoid colloquialisms and abbreviations.

Record only one diagnosis, sign, or symptom per event field on the AE eCRF (eg, nausea and vomiting should not be recorded in the same entry, but as 2 separate entries).

In order to classify AEs and diseases, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

10.3.1.1 Diagnosis versus Signs and Symptoms

Using accepted medical terminology, enter the diagnosis (if known). If not known, enter the most medically significant sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, then this diagnosis should be entered on the AE form, replacing the original entries where appropriate.

10.3.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF. However, medically important events that may be linked and/or separated in time should be recorded as independent events on the eCRF. For example, if severe hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

10.3.1.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such an event should be recorded only once on the eCRF unless its severity increases or decreases (in which case it should be recorded again on the AE eCRF).

A recurrent AE is one that occurs and resolves between subject evaluation time points, but then subsequently recurs. Each recurrence of the AE should be recorded on the AE eCRF.

10.3.1.4 Hypotension

If an asymptomatic drop in blood pressure meets the protocol definition of AE per clinical judgment of the reporter, report the event as "blood pressure decreased." If the drop in blood pressure is associated with signs or symptoms, complete the symptomatic hypotension eCRF and use the following guidance to report the corresponding AE eCRF: If a unifying diagnosis is available to explain the event of hypotension, report the diagnosis as an AE and capture signs and symptoms on the symptomatic hypotension eCRF page. If no other unifying diagnosis is available, report "hypotension" as the event and capture signs and symptoms on the symptomatic hypotension eCRF page.

10.3.1.5 Injection Site Reactions

If an injection site reaction is associated with a single sign or symptom, report the event on AE eCRF page (eg, redness at injection site, AE is injection site redness). If the injection site reaction is associated with multiple signs or symptoms, report injection site reaction as the adverse event on the AE page, and individual signs and symptoms will be reported on the ISR eCRF page (eg, if the subject experiences redness and induration, report "Injection site reaction" on the AE page, and in the corresponding Injection eCRF page, report erythema and induration).

10.3.1.6 Abnormal Laboratory Values

A data transfer file from the central laboratory will provide laboratory test results.

Any laboratory result abnormality fulfilling the criteria for a SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

A clinical laboratory abnormality should be documented as AE if it is not otherwise refuted by a repeat test to confirm the abnormality and any one or more of the following conditions are met:

- Accompanied by clinical symptoms.
- Leading to a change in study medication (eg, interruption or permanent discontinuation).
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management (eg, discontinuation of study drug, more frequent follow-up assessments, further diagnostic investigation).

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication that falls outside the laboratory reference range and meets the clinical significance criteria.

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria (these will be analyzed and reported as laboratory abnormalities), those that are considered AEs of the type explicitly exempted by the protocol, or those which are a result of an AE that has already been reported.

10.3.1.7 Pre-existing Conditions

A pre-existing condition is one that is present at the screening visit. Such conditions should be recorded as medical history on the appropriate eCRF.

A pre-existing condition should be recorded as an AE or SAE during the study only if the frequency, intensity, or character of the condition worsens during the study period. It is important to convey the concept that a pre-existing condition has changed by including applicable language in the verbatim description of the event (eg, more frequent headaches).

10.3.1.8 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition (refer to Section 10.3.1.7). During the study, any new clinically significant findings and/or abnormalities discovered on physical examination that meet the definition of an AE (or an SAE) must be recorded and document as an AE or SAE on the AE eCRF.

10.3.1.9 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol (refer to Section 10.1.2).

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include planned hospitalizations or prolonged hospitalizations to:

- Perform a protocol-mandated procedure.
- Undergo a diagnostic or elective surgical procedure planned prior to study enrollment or for a pre-existing medical condition that has not changed.
- Receive scheduled therapy (study drug or otherwise) for the study indication.

10.3.1.10 Deaths

All deaths that occur during the AE reporting period (refer to Section 10.2.1), regardless of attribution, will be recorded on the AE eCRF and expeditiously reported to the Sponsor as an SAE.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” or “Death of Unknown Cause” on the eCRF. If the death is attributed to progression of the disease or condition being studied, record progression of achondroplasia as the SAE term on the eCRF.

10.3.1.11 Pregnancy

Although not an AE per se, pregnancy in either a subject or the partner of a subject taking trial medication should be reported to facilitate outcome monitoring by the Sponsor.

The reporting period for pregnancy in a subject or partner begins following the first dose of study drug and continues until 12 weeks after the final dose of study drug. Pregnancy events must be reported within 24 hours of the site becoming aware of the pregnancy by faxing the Pregnancy Form in the study reference materials to BioMarin Pharmacovigilance (BPV).
In addition, pregnancy in a subject is also reported on the End of Study eCRF.
The investigator must make every effort to follow the subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up in the eCRF. In the event of pregnancy in the partner of a study subject, the investigator

should make every reasonable attempt to obtain the woman's consent for release of protected health information.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these to be medically significant), recorded on the eCRF, and expeditiously reported to the Sponsor as an SAE.

10.4 Reporting Requirements

The Sponsor is responsible for identifying, preparing, and reporting all suspected unexpected serious adverse reactions (SUSARs) to the relevant competent authorities, ethics committees, and investigators in accordance with requirements identified in the Clinical Trials Regulations.

10.4.1 Expedited Reporting Requirements

All SAEs that occur during the course of the AE Reporting Period (refer to Section 10.2.1), whether or not considered related to study drug, must be reported by faxing the study-specific SAE Report Form to BPV within 24 hours of the site becoming aware of the event. Each SAE must also be reported on the appropriate eCRF. Investigators should not wait to collect information that fully documents the event before notifying BPV of an SAE. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by BioMarin as soon as it becomes available.

The study SAE reporting period is as follows: after informed consent but prior to initiation of study treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, all SAEs must be reported through 4 weeks following either the last administration of study drug or the Early Termination visit, whichever is longer.

10.4.2 IRB/EC Reporting Requirements

Reporting of SAEs to the IRB/IEC/REB will be done in compliance with the standard operating procedures and policies of the IRB/IEC/REB and with applicable regulatory requirements. Adequate documentation must be obtained by BioMarin showing that the IRB/IEC/REB was properly and promptly notified as required.

10.5 Follow-up of Subjects after Adverse Events

The investigator should follow all unresolved AEs SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Outcome of AEs and resolution of SAEs (with dates) should be documented on the AE eCRF and in the subject's medical record to facilitate source data verification.

For some SAEs, the Sponsor may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (eg, hospital discharge summary, consultant report, autopsy report) deemed necessary to appropriately evaluate the SAE report.

10.6 Post-Study Adverse Events

At the last scheduled visit, the investigator should instruct each subject to report, to the investigator and/or to BPV directly, any subsequent SAEs that the subject's personal physician(s) believes might be related to prior study treatment.

The investigator should notify the study Sponsor of any death or SAE occurring at any time after a subject has discontinued or terminated study participation, if the investigator believes that the death or SAE may have been related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that participated in this study.

10.7 Urgent Safety Measures

The regulations governing clinical trials state that the sponsor and investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subject s, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

The Sponsor is responsible for identifying, preparing and reporting all suspected unexpected serious adverse reactions (SUSARs) to the relevant competent authorities, ethics committees

and investigators in accordance with the requirements identified in the Clinical Trials Regulations.

The reporting period for these events, which may require the implementation of urgent safety measures, is the period from the time of signing of the ICF through the completion of the last study visit or at the Early Termination visit. Investigators are required to report any events which may require the implementation of urgent safety measures to BioMarin within 24 hours.

Examples of situations that may require urgent safety measures include discovery of the following:

- Immediate need to revise the IP administration (eg, modified dose amount, frequency not defined in protocol).
- Lack of study scientific value, or detrimental study conduct or management.
- Discovery that the quality or safety of the IP does not meet established safety requirements.

10.8 BioMarin Pharmacovigilance Contact Information

Contact information for BioMarin Pharmacovigilance is as follows:

BioMarin Pharmaceutical Inc.

Address:	105 Digital Drive Novato, CA 94949 USA
Phone:	(415) 506-6179
Fax:	(415) 532-3144
E-mail:	drugsafety@bmrn.com

The investigator is encouraged to discuss with the medical monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the medical monitor is as follows:

Name:	PI , MD
Address:	10 Bloomsbury Way London WC1A 2SL
Phone:	PI
Fax:	PI
E-mail:	PI PI

11 APPROPRIATENESS OF MEASUREMENTS

The parameters to be evaluated in this study reflect the combined experience in the clinical study 111-202 and reflect the need to further define the efficacy and safety profile of BMN 111 in the context of ACH, a complex skeletal dysplasia disorder with multiple clinical manifestations.

The efficacy parameters to be evaluated in this study reflect the sponsor's experience in the clinical study 111-202 and of previous studies of approved growth products (Kemp, 2009; Bright,2009). Evaluation of the parameters proposed in this study will document the effect of BMN 111 treatment on AGV in children with ACH and are relevant to assessing the medical complications of ACH in this patient population.

The PK assessments in this study are generally recognized as reliable, accurate, and relevant.

Bone-related biomarkers and other biochemical markers of the pharmacological activity of BMN 111 in the blood or urine, as well as genomic biomarkers, are exploratory assessments.

12 STUDY PROCEDURES

An ICF must be signed and dated by the subject (or the subject's legally authorized representative if the subject is less than age of majority), the investigator or designee and witness (if required) before any study-related procedures are performed.

12.1 Screening Visit (Day -30 to Day -1)

Screening Visit procedures and assessments that should be performed are noted below.

- Optional parental height assessment (NOTE: can be done at any point in the study).
- Demographics, medical history, including ACH-related history.
- Diagnostic genetic testing (if needed).
- Physical examination.
- Tanner Stage of Pubertal Development.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Anthropometric measurements.
- Weight.
- HRQoL questionnaires (PedsQL and QoLISSY).
- Functional Independence Assessment (WeeFIM).
- Child Behavior Checklist (CBCL).
- Hip clinical assessment.
- Hip imaging via pelvis X-ray (anterior-posterior [AP] view).
- Sleep study (optional).
- ECG.
- Echocardiogram.
- Clinical labs (hematology, chemistry, and urinalysis).
- Thyroid function tests.
- 25-hydroxy Vitamin D.
- Salivary cortisol.

- Serum prolactin.
- FSH/LH.
- DXA (BMD and BMC of whole body less head, spine).
- Hand and wrist X-ray (PA view, left side).
- Bilateral lower extremity X-rays (AP and lateral views).
- Lumbar spine X-rays (AP and lateral views).
- Concomitant medications.
- Adverse events.

12.2 Treatment Visits

12.2.1 Day 1 (no visit window)

- Physical examination.
- Menstrual history in female subjects (if applicable)
- Pregnancy test (urine or serum) for female subjects who have begun menses or are≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Anthropometric measurements.
- Weight.
- ECG (pre-dose and post-dose).
- Clinical labs (hematology, chemistry, and urinalysis).
- Anti- BMN 111 immunogenicity.
- Bone metabolism blood biomarkers.
- Bone metabolism urine biomarkers.
- BMN 111 activity urine biomarkers (cyclic guanosine monophosphate [cGMP]).
- Urine chemistry.
- PK (full).
- Injection site photos (optional).
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.

- Adverse events.
- Procedures/interventions/surgeries.

12.2.2 Day 2 (no visit window)

- Menstrual history in female subjects.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- BMN 111 activity urine biomarkers (cGMP).
- Urine chemistry.
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.2.3 Day 3 (no visit window)

- Menstrual history in female subjects (if applicable).
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Weight.
- BMN 111 activity urine biomarkers (cGMP).
- Urine chemistry.
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.2.4 Day 10 (±1 day)

- Physical examination.
- Menstrual history in female subjects (if applicable).
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Weight.
- ECG (post-dose).

- Clinical labs (hematology, chemistry, and urinalysis).
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.2.5 Week 6 (±7 days)

- Physical examination.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Weight.
- Clinical labs (hematology, chemistry, and urinalysis).
- BMN 111 activity urine biomarkers (cGMP).
- Urine chemistry.
- Genomic biomarkers (optional).
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.2.6 Week 13 (± 7 days)

- Physical examination.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are ≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Anthropometric measurements.
- Weight.

- ECG (post-dose).
- Clinical labs (hematology, chemistry, and urinalysis).
- Bone metabolism blood biomarkers.
- Bone metabolism urine biomarkers.
- Anti-BMN 111 immunogenicity assessments.
- PK (partial).
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.2.7 Week 26 (±7 days)

- Physical examination.
- Tanner Stage of Pubertal Development.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are ≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Anthropometric measurements.
- Weight.
- HRQoL questionnaires (PedsQL and QoLISSY).
- Functional Independence Assessment (WeeFIM).
- Child Behavior Checklist (CBCL).
- Hip clinical assessment.
- ECG (post-dose).
- Clinical labs (hematology, chemistry, and urinalysis).
- 25-hydroxy Vitamin D.
- Salivary cortisol.
- Serum prolactin.

- FSH/LH.
- Anti-BMN 111 immunogenicity assessments.
- Bone metabolism blood biomarkers.
- Bone metabolism urine biomarkers.
- BMN 111 activity urine biomarkers (cGMP).
- Urine chemistry.
- PK (full).
- DXA (BMD and BMC of whole body less head, spine).
- Hand and wrist X-ray (PA view, left side).
- Bilateral lower extremity X-rays (AP and lateral views).
- Injection site photos (optional).
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.2.8 Week 39 (±7 days)

- Physical examination.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Anthropometric measurements.
- Weight.
- ECG (post-dose).
- Clinical labs (hematology, chemistry, and urinalysis).
- Anti-BMN 111 immunogenicity assessments.
- Bone metabolism blood biomarkers.
- Bone metabolism urine biomarkers..

- PK (partial).
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.2.9 Week 52 (±7 days)

- Physical examination.
- Tanner Stage of Pubertal Development.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Anthropometric measurements.
- Weight.
- HRQoL questionnaires (PedsQL and QoLISSY).
- Functional Independence Assessment(WeeFIM).
- Child Behavior Checklist (CBCL).
- Hip clinical assessment.
- Sleep study (optional).
- ECG (post-dose).
- Clinical labs (hematology, chemistry, and urinalysis).
- Thyroid function tests.
- 25-hydroxy Vitamin D.
- Salivary cortisol.
- Serum prolactin.
- FSH/LH.
- Anti-BMN 111 immunogenicity assessments.
- Bone metabolism blood biomarkers.

- Bone metabolism urine biomarkers.
- Genomic biomarkers (optional).
- BMN 111 activity urine biomarkers (cGMP).
- Urine chemistry.
- PK (full).
- DXA (BMD and BMC of whole body less head, spine).
- Hand and wrist X-ray (PA view, left side).
- Bilateral whole leg, AP only.
- Lumbar spine X-rays (AP and lateral views).
- Injection site photos (optional).
- Concomitant medications.
- BMN 111 or placebo administration.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.3 Week 56 (±7 Days) Safety Follow-Up Visit

- Physical examination.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- ECG.
- Clinical labs (hematology, chemistry, and urinalysis).
- Anti-BMN 111 immunogenicity assessments.
- Bone metabolism blood biomarkers.
- Bone metabolism urine biomarkers.
- Concomitant medications.
- Adverse events.
- Procedures/interventions/surgeries.

12.4 Early Termination

- Physical examination.
- Tanner Stage of Pubertal Development.
- Menstrual history in female subjects (if applicable).
- Pregnancy test (urine or serum) for female subjects who have begun menses or are≥ 10 years old.
- Vital signs (body temperature, heart rate, BP, respiratory rate).
- Anthropometric measurements (only if the subject discontinues after Week 6).
- Weight.
- Hip clinical assessment.
- Sleep study (only if Early Termination visit occurs after Week 26 and subject has had a previous sleep study during the trial, ie, has entered the sleep sub-study).
- ECG.
- Clinical labs (hematology, chemistry, and urinalysis).
- Thyroid function tests.
- 25-hydroxy Vitamin D.
- Salivary cortisol.
- Serum prolactin.
- FSH/LH.
- Anti-BMN 111 immunogenicity assessments.
- Bone metabolism blood biomarkers.
- Bone metabolism urine biomarkers.
- DXA (BMD and BMC of whole body less head, spine (only if subject discontinues after 9 months).
- Hand and wrist X-ray (PA view, left side) (obtained only if the subject discontinues after 9 months).
- Bilateral X-rays of lower extremity including AP and lateral views (only if subject discontinues after 9 months).
- Lumbar spine X-rays (AP and lateral views) (only if subject discontinues after 9 months).
- Injection site photos (only if an injection is given at this visit).

- Concomitant medications.
- BMN 111 or placebo accountability.
- Adverse events.
- Procedures/interventions/surgeries.

12.5 Contact for Study Follow-up

Contact by a study staff member to the caregiver will be required after the Week 6 visit every 4 weeks (±10 days) when there are no study visits or contact in the preceding 4 weeks. During these contacts, study staff will ask about dose administration and seek information on AEs and SAEs by specific questioning. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

13 DATA QUALITY ASSURANCE

BioMarin personnel or designees will visit the study site prior to initiation of the study to review with the site personnel information about the IP, protocol and other regulatory document requirements, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

At visits during and after the study, a CRA will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of data on CRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records.

Sites will enter study data into eCRFs into the study electronic data capture (EDC) system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications. Additional subject-reported study data may be entered into the study EDC system via electronic diary.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis and the final version must be finalized prior to database lock. The SAP will overrule any differences with the analytical plan described in the protocol . Unless otherwise stated, all analyses will be performed using SAS v. 9.4.

14.1.1 Interim Analyses

No formal futility/efficacy interim analyses are planned for this study.

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Because the completeness of the data affects the integrity and accuracy of the final study analysis, every effort will be made to ensure complete, accurate and timely data collection and, therefore, avoid missing data. In addition, a subject who prematurely discontinues study drug should be asked if they are willing to continue to participate in the study assessments for remaining duration of the study, as long as in the judgment of the investigator such continued participation would not detrimentally affect the health, safety, or welfare of the subject.

No missing data will be imputed for any analysis, except for unless otherwise specified for the efficacy analyses or for the missing dates for AEs and concomitant medications. Missing dates or partially missing dates will be imputed conservatively to ensure that an AE is considered treatment emergent and has the longest possible duration, if the partial information available indicates that the AE is likely treatment emergent.

Additional details regarding the handling of missing data will be provided in the SAP.

14.2 Efficacy Analysis

All efficacy analysis will be done on the efficacy population defined in Section 14.7.1

14.2.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in AGV at the 12–month time point. For a given interval [Date1, Date2], the AGV is defined as follows:

$$\text{AGV} = \frac{\text{StandingHeight at Date2} - \text{StandingHeight at Date1}}{\text{Interval Length (Days)}} \times 365.25$$

where the interval length in days is calculated as Date2 – Date1. AGV will be calculated for the following visits/intervals:

- Baseline: [Date of last height measurement in study 901 at least 6 months prior to Date of Day 1 visit in study 301, Date of Day 1]
- Week 13: [Date of Day 1, Date of Week 13]
- Week 26: [Date of Day 1, Date of Week 26]
- Week 39: [Date of Day 1, Date of Week 39]
- Week 52 (12-month): [Date of Day 1, Date of Week 52]

The baseline of the AGV is established in the natural history study of Study111-901, based on the standing height measurements in the last 6 months prior to enrollment to Study 111-301.

The primary estimand is the difference in mean change from baseline in AGV at 12-month time point between the BMN 111 group and the placebo group. The estimand is defined on all randomized subjects who received at least one dose of double-blinded BMN 111 or placebo. The least-squares (LS) means of the change from baseline in AGV at 12-month will be used to estimate the primary estimand for the BMN 111 group and the placebo group based on an analysis of covariance (ANCOVA) model, with fixed-effect terms including treatment group, sex, and Tanner stage, and age and the baseline AGV as covariates. The following primary hypothesis will be tested (two-tailed):

> *H0: Difference in mean AGV change from baseline at 12 months between BMN 111 group and the placebo group = 0*
>
> *Ha: Difference in mean AGV change from baseline at 12 months between BMN 111 group and the placebo group ≠ 0*

Subjects who discontinue from the study drug will be encouraged to remain in the study and their non-missing height measurements will continue to be used in calculating the AGV and to be included in the analysis per intend to treat principle. In the event that missing data does occur despite all efforts, missing standing height will be imputed based on multiple imputation (MI) with pattern-mixture models (Little 1993; Molenberghs 2007) implemented in Proc MI of SAS where the missing, unobserved observations of the standing height are assumed to follow missing not at random (MNAR) mechanism. Each imputation will require sufficient standing height data collected from the subjects in the same randomization group who also discontinue treatment prematurely (but remain in the study), referred to as off-treatment data, as these subjects will be used as the reference data for MI. Ten (10) sets of imputations of the missing standing heights will be constructed from MI and the AGV at the missing time points will be calculated based on these 10 sets of data. For

each subject whose value is imputed, the 10 imputed values will be provided in a data listing that will be included in the appendix of the CSR. The above-mentioned Mixed model will be applied to the 10 imputed data sets from MI. The analysis results based on the 10 imputed datasets will be summarized using Proc MIANALIZE in SAS.

In the event there is insufficient data to perform the imputations for subjects who discontinue the treatment early, then the mixed model will be applied without multiple imputations. The study is considered positive if the primary test is significant in favor of BMN 111.

The AGV and its change from baseline at each scheduled post-treatment visit will be summarized at Week 26 and Week 52 using descriptive statistics (mean, SD, median, Q1,Q3, minimum, and maximum) per group.

14.2.2 Secondary Efficacy Analyses

The key secondary efficacy endpoints are the change from baseline in height Z-score and the change from baseline in upper:lower body segment ratio. The estimand of the secondary efficacy endpoints is the difference in mean change from baseline in the corresponding endpoint at 12-month time point between the BMN 111 group and the placebo group (all randomized subjects).

The measurement of standing height at each scheduled visit will be converted to age-and sex-appropriate standard score, also referred to as Z-score, by comparison with normal reference standards (not ACH). The height Z-score and its change from baseline will be summarized using descriptive statistics. The null hypothesis of no difference between the BMN 111 group and the placebo group in the mean change from baseline in the height Z-score at 12-month time point will also be tested based on 10 imputed data sets using an ANCOVA model, with fixed-effect terms including treatment group, sex, and Tanner stage, and age and the baseline Z-score as covariates. The analysis results based on the 10 imputed datasets will be summarized using Proc MIANALIZE in SAS. The upper:lower body segment ratio and its change from baseline will be similarly summarized and tested.

Additional secondary efficacy endpoints include change from baseline in body proportions of the extremities, HRQoL (QoLISSY, PedsQL) scores, and functional independence (WeeFIM) scores.

Details regarding the analysis methods for the additional secondary endpoints will be provided in the SAP.

14.2.3 Controlling for Multiplicity

The overall type I family-wise error rate for testing the primary and secondary efficacy endpoints will be controlled at the 0.05 significance level using the following 3-step serial gatekeeping multiple comparisons procedure (MCP). Following this MCP, advancement to the next step will only occur if the null hypotheses within a step and the previous step(s) are all rejected at the significance level of 0.05 in favor of BMN 111. If any null hypothesis within a step is not rejected or is rejected but not in favor of BMN 111, the hypothesis tests corresponding to all subsequent steps will not be considered statistically significant.
All hypothesis tests will be two-sided.

1. The first step will be the test comparing the BMN 111 group to the placebo group for the primary efficacy endpoint, the change from baseline in AGV at 12-month time point. If the null hypothesis is not rejected (ie, p-value > 0.05) or is rejected but not in favor of BMN 111, all subsequent statistical tests will not be considered statistically significant. The study is considered positive if the primary test is significant in favor of BMN 111.
2. The second step will be the test comparing the BMN 111 group to the placebo group for the secondary efficacy endpoint, the change from baseline in height Z-score at 12-month time point. If the null hypothesis is not rejected (ie, p-value > 0.05) or is rejected but not in favor of BMN 111, the subsequent statistical test will not be considered statistically significant.
3. The third step will be the tests comparing the BMN 111 group to the placebo group for the secondary efficacy endpoint, the change from baseline in upper:lower body segment ratio at 12-month time point at a significance level of 0.05.

By-subject listings will also be provided for efficacy endpoints.

14.2.4 Sensitivity Analyses

To assess the robustness of the primary analysis result, sensitivity analyses such as the following will be performed:

Mixed Model with Repeated Measures (MMRM)

The primary null hypothesis of no difference between the BMN 111 group and the placebo group in the mean change from baseline in AGV at the 12-month time point will be tested using a mixed model with repeated measures (MMRM), with fixed-effect terms including treatment group, visit, sex, Tanner stage, and interaction of treatment group and visit, and age and the baseline AGV as covariates, repeated over visits. All available AGV assessments from all scheduled visits up to 12-month will be used in the MMRM analysis.

MI Based on Missing At Random (MAR) Assumption

The sensitivity analyses will be based on the MI technique as proposed by Little and Rubin (1987) implemented in PROC MI of SAS where the missing, unobserved observations of the response variable are assumed to follow missing at random (MAR) mechanism. The MI procedure will be directly applied to standing height and AGV will be calculated based on imputed height. The ANCOVA model described in the primary analysis will be performed separately for each imputation dataset and a summary overall imputed samples will be provided for each analysis.

Random Coefficients Model

The mean change from baseline (Day 1) in height at 12-month time point will be estimated for both the treatment group and the placebo group based on a MMRM, with fixed-effect terms including treatment group, visit, sex, Tanner stage, and age and the baseline height as covariates, and random-effect terms of the intercept and the subject*visit interaction. For each randomized group, an AGV at 12-month time point will be defined as the mean change from baseline in height at 12-month from the MMRM model above.

ANCOVA on Completers

In this sensitivity analysis, the estimand will be the difference of the means of the change from baseline in AGV at 12-month observed from subjects who have non-missing observation at 12-month between the two randomized groups. No missing data will be imputed. The LS means of the change from baseline in AGV at 12-month will be estimated for both the randomized groups by applying the mixed model described in the primary analysis. In this analysis, only subjects with observed AGV change from baseline at 12-month will be included. No extrapolation or imputation will be performed for missing 12-month standing height measurements.

14.2.5 Exploratory Analyses

Exploratory endpoints include sleep apnea assessment, BMN 111 activity biomarkers and genomic biomarkers.

Details regarding the analysis methods for the exploratory endpoints will be provided in the SAP.

14.3 Pharmacokinetic Analyses

Blood samples from subjects randomized to receive BMN 111 will undergo pharmacokinetic testing.

For subjects randomized to BMN 111, PK parameters generated over the course of the study will be evaluated and summarized with descriptive statistical measures (mean, standard deviation, percentage of coefficient of variation [CV%], minimum, median and maximum). Correlative analyses of some of the PK parameters with efficacy, safety and immunogenicity measures may be conducted.

14.4 Safety Analysis

All randomized subjects who receive at least one dose of double-blinded BMN 111 or placebo in this study will be included in the safety analysis. The safety analysis will be performed on safety population as defined in Section 14.7.2 and will be considered descriptive.

All AEs will be coded using the most current version of MedDRA will be used by the Sponsor to assign system organ class and preferred term classification to events and diseases, based on the original terms entered on the CRF.

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment (as assessed by investigator), and severity. All AEs, including SAEs and AEs that lead to permanent discontinuation from the study and from the study treatment, will be listed. Hypersensitivity reactions and symptomatic hypotension are of interest, and the percentage of subjects who report these AEs will be presented. Hypersensitivity reactions will be defined in the SAP.

Clinical laboratory data will be summarized by the type of laboratory test. For each clinical laboratory test, descriptive statistics will be provided on baseline as well as all subsequent visits.

Descriptive statistics for other safety endpoints such as vital signs, ECG results, X-ray and DXA assessments of bone morphology and quality, clinical hip assessment, CBCL, anti-BMN 111 immunogenicity assessments, and bone metabolism biomarkers, will also be provided. Detailed statistical methods will be provided in the SAP. All other safety measures including laboratory tests, vital signs, ECG, X-ray and DXA assessments, clinical hip assessment, and anti-BMN 111 immunogenicity (discussed in the next section) will be summarized descriptively by group, listings will be provided for these safety endpoints.

14.5 Immunogenicity Analysis

Immunogenicity will be summarized as change from baseline as well as by study time point in subjects randomized to receive BMN 111 or placebo. Results will be summarized as

incidence and titer for all cohorts. Additionally, immunogenicity may be assessed for correlations with measures of safety, PK, and efficacy.

14.6 Determination of Sample Size

With 55 subjects planned in each of the two randomized groups (one BMN 111 dose group and one placebo group), the power to detect a difference of 1.75 cm/year between the BMN 111 group and the placebo group in change from baseline in AGV at 12 months is approximately 90%, assuming that the pooled standard deviation of the change from baseline in AGV is 2.80, using a two-sided two-sample t-test at a 0.05 significance level. The power calculation is based on data from Study 111-202 (a phase 2, open-label, sequential cohort dose-escalation study) and Study 111-901 (a natural history study for pediatric subjects with achondroplasia).

14.7 Analysis Populations

14.7.1 Efficacy Population

All randomized subjects who receive at least one dose of double-blinded BMN 111 or placebo in this study.

14.7.2 Safety Population

All randomized subjects who receive at least one dose of double-blinded BMN 111 or placebo in this study.

14.7.3 PK Population

All randomized subjects who receive at least one dose of double-blinded BMN 111 in this study and have at least one evaluable PK concentration.

14.8 Changes in the Conduct of the Study or Planned Analyses

Only BioMarin may modify the protocol. Any change in study conduct considered necessary by the investigator will be made only after consultation with BioMarin, who will then issue a formal protocol amendment to implement the change. The only exception is when an investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC/REB must be sought, and the investigator should inform BioMarin and the full IRB/IEC/REB within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/IEC/REB must review and approve all protocol amendments. Protocol amendments that have an impact

on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by BioMarin and the IRB/IEC/REB, and all active subjects must again provide informed consent.

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

15 DATA MONITORING COMMITTEE

In addition to safety monitoring by BioMarin personnel, an independent DMC will act as an advisory body to BioMarin and will monitor the safety data and PK of subjects in the study. The DMC will include independent experts.

DMC data review will occur at regular time periods during the course of the study per the DMC charter (or ad hoc, if indicated).

16 COMPENSATION AND INSURANCE

There will be no charge to study subjects to be in this study. BioMarin will pay all costs of tests, procedures, and treatments that are part of this study. In addition, after IRB/EC/REB approval, BioMarin may reimburse the cost of travel for study-related visits. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort, whether or not related to the study subject's disease that are not part of this study. Costs associated with hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP or by procedures performed as part of the study. Any subject who experiences a study-related injury should be instructed by the investigator to seek medical treatment at a pre-specified medical institution if possible, or at the closest medical treatment facility if necessary. The subject should be given the name of a person to contact to seek further information about, and assistance with, treatment for study-related injuries.
The treating physician should bill the subject's health insurance company or other third party payer for the cost of this medical treatment. If the subject has followed the investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, BioMarin will comply with the law.

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic case report forms will be provided for each subject. The investigator must review and electronically sign the completed eCRF casebook to verify its accuracy.

eCRFs must be completed using a validated web-based application. Study site personnel will be trained on the application and will enter the clinical data from source documentation, except in the instances when electronic subject reported data is transmitted directly to EDC, as referenced in the study specific vendor management plan.

Unless explicitly allowed in the CRF instructions, blank data fields are not acceptable.

In the event of an entry error, or if new information becomes available, the value will be corrected by deselecting the erroneous response and then selecting or entering the factual response. In compliance with 21 CFR Part 11, the system will require the personnel making the correction to enter a reason for changing the value. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction and the identity of the operator.

BioMarin's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representative) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If an investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" (SDV). Electronic subject-reported data transmitted directly into EDC will not be SDV'd or queried.

If an error is discovered at any time or a clarification is needed, the CRA, or designee, will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Before a subject's eCRF casebook can be locked, data fields must be source data verified and all queries closed. Refer to the Clinical Monitoring Plan for details on which fields must be

source data verified. The Data Manager, or designee, will then set the status of the forms, visits, and the entire casebook to Locked. The investigator will then electronically sign the casebook, specifying that the information on the eCRFs is accurate and complete. As part of site close-out activities, an electronic copy of each site's casebooks will be copied to a compact disc or digital versatile disc and sent to each study site for retention with other study documents.

18 STUDY MONITORING AND AUDITING

Qualified individuals designated by BioMarin will monitor all aspects of the study according to GCP and standard operating procedures for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records, of the study subjects, and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by BioMarin or its designees.

Members of BioMarin's GCP Compliance Department or designees may conduct an audit of a clinical site at any time before, during, or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an inspection of the study. If informed of such an inspection, the investigator should notify BioMarin immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

19 RETENTION OF RECORDS

The investigator must retain all study records required by BioMarin and by the applicable regulations in a secure and safe facility. The investigator must consult a BioMarin representative before disposal of any study records, and must notify BioMarin of any change in the location, disposition or custody of the study files. The investigator /institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (eg, subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the U.S. or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator /institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a BioMarin agreement. BioMarin must be notified and will assist with retention should investigator /institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of BioMarin to inform the investigator /institution as to when these documents no longer need to be retained.

20 USE OF INFORMATION AND PUBLICATION

BioMarin recognizes the importance of communicating medical study data and therefore encourages the publication of these data in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between BioMarin and the investigator/Institution. Consideration for authorship of all publications will be based on compliance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals ("Uniform Requirements") of the International Committee of Medical Journal Editors (http://www.icmje.org/about-icmje/faqs/icmje-recommendations/) and good publication practices.

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572, the investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IRB review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/EC/REB complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/EC/REB. Additionally, he or she will not make any changes in the research without IRB/EC/REB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

23 SIGNATURE PAGE

Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with Achondroplasia (ACH)

Protocol Number: 111-301

I have read the forgoing protocol and agree to conduct this study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines, including E6 ICH, as stated in the protocol, and other information supplied to me.

Investigator Signature Date

Printed name: _____

Accepted for the Sponsor:

PI

08.02.2019

Date

Printed name: PI , MD