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

NCT Number: NCT02055157

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 22 August 2016

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol 111-202A4 FINAL 22AUG2016

Protocol 111-202A3 FINAL 26OCT2015

Protocol 111-202A2 FINAL 08MAY2015

Protocol 111-202A1 FINAL 03JUN2014

Protocol 111-202 FINAL 25OCT2013

Protocol 111-202 FINAL French Rev-03 30OCT2015

Protocol 111-202 FINAL French Rev-01 09SEP14

16.1.1 Guidelines

Anthropometric Measurement Procedures V2. 07JUL2015

Elbow Range of Motion Guidelines 05JUN2015

BIOMARIN

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia
Protocol Number:	111-202
Investigational Product:	BMN 111 (modified rhCNP)
IND Number:	111299
European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2013-004137-32
Indication:	Achondroplasia
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 2
Sponsor's Responsible Medical Monitor:	[redacted], MD, PhD Medical Director
Treatment Duration:	Up to 24 months
Study Duration:	25 months
Dose Initial Phase:	Cohort 1: daily morning dose of 2.5 µg/kg Cohort 2: daily morning dose of up to 7.5 µg/kg Cohort 3: daily morning dose of up to 15.0 µg/kg Cohort 4: daily morning dose of 30 µg/kg
Dose Optional, Open-label Extension Phase:	Doses for subjects in Cohorts1-4 may increase up to 30 µg/kg
Date of Original Protocol:	25 October 2013
Date of Amendment 1	03 June 2014
Date of Amendment 2	08 May 2015
Date of Amendment 3	26 October 2015
Date of Amendment 4	22 August 2016

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 4

Date: 22 August 2016

RATIONALE AND SUMMARY OF MAJOR CHANGES

This protocol is being revised to make the following changes:

1. Cohort 5 will not be initiated and has been withdrawn from the protocol.

   Rationale: Amendment 2 of Study 111-202 incorporated the option to add two additional cohorts at doses of 30 µg/kg (Cohort 4) and up to 60 µg/kg (Cohort 5). These doses were proposed to achieve exposures expected to result in further increases in annualized growth velocity (AGV) with an acceptable safety profile in children with ACH. Preliminary results from Cohort 4 (30 µg/kg) show a greater than dose-proportional increase in BMN 111 exposure, with a marginal improvement in both absolute AGV and change from baseline AGV after 6 months of BMN 111 treatment when compared with Cohort 3 (15 µg/kg). Thus, Cohort 5 (with dosing up to 60 µg/kg) will not be pursued.

2. Administrative changes and minor edits for clarity and consistency have been incorporated:
   a. Study Rationale has been revised to make the content more concise [§7.3].
   b. Safety Rationale has been revised to make the content more concise; please refer to the Investigators Brochure for detailed safety information [§7.4.2.2].
   c. Because Cohort 5 has been withdrawn, the number of subjects has been reduced from approximately 46 to approximately 36 subjects [§9.1; §13. 5].
   d. Information regarding blood pressure assessments has been clarified [Schedule of Events; §9.10.4.4.1].

2 SYNOPSIS

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

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

PROTOCOL NUMBER: 111-202

STUDY SITES: Approximately 10 sites

PHASE OF DEVELOPMENT: Phase 2

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. C-type natriuretic peptide (CNP) and its receptor, NPR-B, are key regulators of skeletal growth. Alteration in CNP/NPR-B signaling leads to skeletal-related phenotypes. Reduced or absent CNP expression in mice results in severe dwarfism as a consequence of impaired endochondral ossification (Chusho, 2001, Proc Natl.Acad Sci U.S.A). Individuals who have a mutation in NPR-B that inhibits its function, have a condition known as acromesomelic dysplasia type Maroteaux, characterized by impaired skeletal growth, abnormal growth plates, and short misshapen bones in the extremities (Bartels, 2004, Am.J.Hum.Genet.). Conversely, overexpression of CNP results in overgrowth in mice and humans (Bocciardi, 2007, Hum.Mutat.).

In mice with a *FGFR3* gain-of-function mutation, continuous CNP infusion (Yasoda, 2009, Endocrinology) led to normalization of the dwarfism phenotype, indicating that CNP/NPR-B activation reduced FGFR3 downstream signaling. This work provided the pre-clinical proof of concept that CNP might be a therapy for ACH. However, subcutaneous (SC) administrations of CNP, a preferred clinical route, failed to induce skeletal growth, presumably because of its rapid elimination mediated by NPR-C, a clearance receptor, and by neutral endopeptidase (NEP) proteolysis. CNP half-life is less than 2 minutes after IV administration.

BMN 111 is a recombinant CNP analogue that has been engineered to confer NEP resistance. BMN 111 has a longer half-life, approximately 45 minutes in humans.

The pharmacological activity of BMN 111 was explored in mice (wild-type mice and two mouse models of ACH, a severe, *Fgfr3Y367C/+* model, and a mild *Fgfr3G380R/+* [Ach] model) and in normal rats and monkeys. Partial thanatophoric dysplasia [TD] (Lorget, 2012, Am.J Hum.Genet) or complete [Ach] reversion of the ACH phenotype was observed in these mouse models after BMN 111

administration. Additionally, in wild-type mice rats, and normal monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels.

In Study 111-101, the safety and tolerability of BMN 111 were assessed in adult male volunteers without ACH. This Phase I study was a two-part, double-blind, placebo-controlled study. 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 mean half-life ranged from 40 to 55 minutes.

Study 111-202 is designed as a proof-of-concept study for BMN 111 in children with ACH. The initial phase of this study is 6 months and will allow for assessment of the effect of daily BMN 111 administration on safety, tolerability, growth velocity, absolute growth, and body proportions at doses ranging from 2.5-30 µg/kg given subcutaneously daily. A clinically relevant increase in annualized growth velocity is considered to be in the range of 25%-50% change from baseline, although the targeted increase may be refined based on ongoing comprehensive safety and efficacy review of BMN 111. Additional exploratory endpoints that reflect the medical complications of ACH will also be evaluated.

After completing the initial phase of the study lasting 6 months, subjects may enroll in an optional, open-label extension period of approximately 18 months to commence at the end of the initial phase of the study, making a total study duration of approximately 25 months, including a 1-month safety follow-up visit. The rationale for the extension phase is to assess the long-term safety and tolerability of BMN 111 in children with ACH; and to assess longer-term effects of BMN 111 on growth in these children.

Safety data in monkeys support dosing ACH children at the proposed doses of 30 µg/kg daily with careful monitoring and management of hemodynamic and skeletal changes. To date, clinical data in Study 111-202 demonstrated that BMN 111 was generally well tolerated at doses up to 30 µg/kg without evidence of abnormal growth or significant cardiovascular effects.

OBJECTIVES:

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

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

The primary objective of the study extension is:

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

The secondary objectives of the study are:

- To evaluate change from baseline in annualized growth velocity following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate changes from baseline in growth parameters following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate changes from baseline in body proportions (upper arm to forearm length, upper

leg to lower leg length, and upper to lower body segment ratios) following daily SC injections of BMN 111 administered for 6 months, and up to 24 months

- To evaluate dose-exposure and PK profiles of BMN 111 in children with ACH following daily SC injections of BMN 111 at each dose level and over multiple days

The exploratory objectives of the study are:

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

STUDY DESIGN AND PLAN:

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

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

Additional safety assessments during this period are electrocardiogram (ECG), physical exams, AE assessment, and clinical labs (Table 9.1.1).

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

- Cohort 1: the first eight subjects will receive 2.5 µg/kg BMN 111.

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

If subjects are tolerating the drug well, caregivers may be able to administer study drug at home if approved by the Investigator, and adequate training is demonstrated. Otherwise, home dosing must be performed by a home health professional. Home health care is not required at any point. In the initial phase, on weeks when caregivers/subjects will not see either a home healthcare professional or a study staff member, a phone call by the study staff member to the caregiver/subject will be required. During the call, study staff will ask the caregiver about correct administration procedures, assess adverse events (AEs), record concomitant medications, and answer questions. During the optional, open-label extension phase, the call frequency will change to every two weeks for the first 6 months of the extension phase and monthly thereafter.

Dose Escalation Plan During the Initial 6 Months of the Study

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

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

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 and PK (when available) of subjects in the study. The DMC will include independent experts and key opinion leaders in fields that may include, but not limited to: ACH, natriuretic peptides, bone growth, cardiology, radiology, clinical pharmacology, and biostatistics. The DMC will make recommendations for stopping or continuing the study on a subject level and/or on a cohort level per the pre-specified stopping criteria. The DMC may also provide recommendations for dose modifications as needed for each cohort.

Individual Subject Stopping Criteria

For individual subjects, temporary dosing suspension, permanent discontinuation of dosing, or, in exceptional circumstances, dose reduction will be considered and DMC will be informed (at a minimum) if any of the following occur:

- Any treatment-emergent adverse event (TEAE) at least Grade 3 assessed by the Investigator and/or Sponsor Medical Monitor
- Any two TEAEs Grade 2 experienced by the same subject within 1 week, including two symptomatic hypotension events within 1 week (non-urgent medical intervention indicated) or any Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Prolongation of QTc-F interval to more than 500 millisecond (msec), ventricular tachycardia

greater than five beats

- Any clinically significant worsening of existing disproportionate growth, as determined by physical measurement ratios and/or Investigator assessments based on imaging, measurement or clinical observation findings
    - Upper arm to forearm length ratio
    - Upper leg to lower leg length ratio
    - Upper to lower body segment ratio
- Clinically significant worsening of bone morphology as evidenced by development of tibial bowing, or worsening of existing tibial bowing as observed via clinical or radiographic assessment
- Clinically significant worsening of elbow joint range of motion based on clinical assessment and on goniometry measurements of flexion-extension
- Findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as decided by principal investigator and in consultation with sponsor medical monitor and orthopedic specialist (if needed).

If the subject meets any stopping criteria, after Investigator consultation with the BioMarin Medical Monitor and DMC, the subject may be re- challenged at the same dose. If the subject meets stopping criteria on re-challenge or if re-challenge at same dose is not clinically indicated, other options that may be considered include:

- Re-challenge at lower dose with consideration given to upward titration to tolerated dose/cohort dose
- Permanent treatment discontinuation (with an option of ongoing assessment in the study)

Cohort Stopping Criteria

For any open cohort and all higher dose cohorts, temporary dosing suspension or dose reduction will be considered and DMC review will be conducted (at a minimum) if any of the following occur:

- Any two subjects within a cohort have treatment-emergent AE at least Grade 3; any two subjects have two symptomatic hypotension events within 1 week each Grade 2 (non-urgent medical intervention indicated); or any two subjects have a Grade 3 hypotension event (urgent medical intervention or hospitalization indicated) as assessed by the Investigator and/or Sponsor Medical Monitor
- Any one subject with any treatment-emergent AE Grade 4 or 5 assessed by the Investigator and/or Sponsor Medical Monitor
- Any two subjects within a cohort have prolongation of QTc-F interval to more than 500 msec, ventricular tachycardia greater than five beats
- Any two subjects within a cohort have clinically significant worsening of existing disproportionate growth, as determined by physical measurement ratios and/or Investigator assessments based on imaging, measurement or clinical observation findings:
    - Upper arm to forearm length ratio

- Upper leg to lower leg length ratio
- Upper to lower body segment ratio

- Any two subjects within a cohort exhibit clinically significant worsening of bone morphology as evidenced by development of tibial bowing, or worsening of existing tibial bowing as observed via clinical or radiographic assessment
- Any two subjects exhibit clinically significant worsening of elbow joint range of motion based on clinical assessment and on goniometry measurements of flexion-extension
- Any two subjects exhibit findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as decided by principal investigator and, if needed, in consultation with sponsor medical monitor and orthopedic specialist (if needed).
- Any other reason DMC advises temporary discontinuation of cohort dosing until further review of safety data is conducted

Sites have 1 business day to report to BioMarin an event that meets individual or cohort stopping criteria. DMC can ask for additional available data while reviewing subject(s) who met individual stopping criteria, or subjects with any other new safety finding. In order to assess significance of the findings, DMC can request to review additional data for other subjects in the cohort, or any other subjects in the study. These additional data include, but are not limited to, physical exam, vital signs, anthropometric measures, ECG, ECHO, and lab results. The DMC will review available, relevant safety data within 5-7 days after BioMarin is apprised of an event. BioMarin will keep all sites informed of enrollment pauses, to ensure that no subjects in the cohort (and all higher cohorts) that are affected by stopping criteria are treated, and no new subjects are enrolled, until the assessment is complete. Based on its review, the DMC may make any of the following recommendations:

- Continue cohort and sequential dosing of cohorts as planned with additional safety monitoring and/or safety reviews as indicated
- Continue current cohort, but higher dose cohorts will receive lower doses than planned
- Decrease cohort dose and decrease doses of subsequent cohorts
- Extend temporary treatment discontinuation until additional data are available and/or further review/consultation occurs
- Permanently discontinue treatment for all cohorts
- Dose additional subjects of the cohort at the same dose

Cohort doses may be changed, based on DMC review of safety and efficacy data, to any dose between 0.5 µg/kg and 30 µg/kg. Any subject who discontinues from study drug will be encouraged to complete assessments as appropriate for the duration of the study (Section 9.3.3).

Optional, Open-label Extension Phase of the Study

In the open-label, optional extension phase, the long-term safety, tolerability, and effects of BMN 111 on growth will be evaluated in children with ACH who have completed an initial 6 months of treatment with BMN 111. At the Day 183/6-month visit, subjects who elect to continue participating in the optional open-label extension phase will be consented for the extension phase. These subjects will receive study drug on Day 184 of the initial phase, which also marks the beginning of the extension phase. Drug treatment will continue without interruption. Subjects who decline to

participate in the extension phase will return at Day 208 for the Safety Follow-Up visit and exit the study.

In the 18-month optional, open-label extension phase, subjects within each cohort will either remain on the same stable dose that they have been receiving during the initial 6 months of treatment, or the dose for all subjects in the cohort (except cohort 4) may be increased based on the following rules:

(1) Initial dose was determined to exhibit suboptimal efficacy on the basis of growth measurements after at least 6 months of treatment based on the review of the data for all subjects in the cohort.

(2) Initial dose, and other doses higher than the initial dose, but lower than the dose to which the cohort is being increased were generally well tolerated for at least 6 months based on review of data for all subjects in the cohort.

(3) The dose to which the subjects in the cohort are being escalated has been previously shown to be well tolerated for at least 10 days of comprehensive outpatient safety monitoring as described in Section 9.1 based on DMC review of the data for all subjects in the cohort previously assigned to the considered dose.

During the optional, open-label extension phase, visits will take place at 2- to 3-month intervals. The site will call the caregiver/subject between visits every two weeks for the first 6 months and every month for the remainder of the study.

The timing of dose adjustments and follow-up visits after adjustment is contingent upon the time at which the dose adjustment was recommended. If the recommendation to adjust the dose is communicated to the sites when the next scheduled visit is $\leq$ 4 weeks away, dose adjustment will be done at the next scheduled visit. If the recommendation to adjust the dose is communicated to the sites when the next scheduled visit is > 4 weeks away, an unscheduled dose adjustment visit will be done within 4 weeks. In both cases, a follow-up visit 4 weeks ($\pm$ 2 weeks) is required after the dose adjustment. The dose adjustment follow-up visit will be scheduled 4 weeks after the dose adjustment visit UNLESS a regularly scheduled visit occurs within the $\pm$ 2-week visit window, in which case a separate follow-up visit will not be required.

DMC data review will occur approximately every 4 months during the optional, open-label extension phase.

Subjects who participate in the open-label extension phase of study 111-202 will have the option to enroll in the long-term extension study 111-205 at the Month 24/Study Completion Visit. Month 24 assessments will serve as Baseline/screening assessments for entry to study 111-205.

NUMBER OF SUBJECTS PLANNED:

Approximately 36 children with ACH, as documented by clinical grounds and genetic testing

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

Inclusion Criteria:

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

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 18 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.

2. 5 to 14 years old, inclusive 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 assessment in Study 111-901 immediately before study entry, and have one documented standing height at least 6 months (+/- 10 days) prior to the screening visit for 111-202
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 a highly effective method of contraception while participating in the study
7. Are ambulatory and able to stand without assistance
8. Are willing and able to perform all study procedures as physically possible
9. Parents or caregivers are willing to administer daily injections to the subjects and complete the required training

Additional Inclusion Criteria for Optional, Open-label Extension Phase:

1. Appropriate written informed consent (and assent, if applicable)

Exclusion Criteria:

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

1. Have hypochondroplasia or short stature condition other than ACH (e.g., trisomy 21, pseudoachondroplasia)
2. Have any of the following:
   a. Hypothyroidism or hyperthyroidism
   b. Insulin-requiring diabetes mellitus
   c. Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others)
   d. Inflammatory bowel disease
   e. Autonomic neuropathy
   f. Recent acute illness associated with volume depletion (e.g., nausea, vomiting, diarrhea) that has not completely resolved prior to the first dose of the study drug
3. Have an unstable condition likely to require surgical intervention during the study (including progressive cervical medullary compression)
4. Growth plates have fused
5. Have a history of any of the following:
   a. Renal insufficiency defined as serum creatinine > 2 mg/dl
   b. Anemia

c. Baseline systolic blood pressure (BP) < 75 millimeters of mercury (mm Hg) or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms i.e., dizziness, fainting) or recurrent symptomatic orthostatic hypotension

d. Cardiac or vascular disease, including the following:

i. Cardiac dysfunction (abnormal echocardiogram [ECHO] including abnormal left ventricle [LV] mass) at Screening Visit
ii. Hypertrophic cardiomyopathy
iii. Pulmonary hypertension
iv. Congenital heart disease with ongoing cardiac dysfunction
v. Cerebrovascular disease
vi. Aortic insufficiency
vii. Clinically significant atrial or ventricular arrhythmias

6. Have the following confirmed ECG findings:
   a. Right or left atrial enlargement or ventricular hypertrophy
   b. PR interval > 200 msec
   c. QRS interval > 110 msec
   d. Corrected QTc-F > 450 msec
   e. Second- or third-degree atrioventricular block
7. Documented Vitamin D deficiency (i.e., concentration of 25-hydroxy-vitamin D in the blood serum occurs at 12 ng/mL or less)
8. Require any investigational agent prior to completion of study period
9. Have received another investigational product or investigational medical device within 30 days 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
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, any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function
12. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the previous 6 months or long-term treatment (> 3 months) at any time
13. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable)
14. Concomitant medication that prolongs the QT/QTc-F interval within 14 days or 5 half-lives, whichever is longer, before the Screening Visit
15. Pregnant or breastfeeding at the Screening Visit or planning to become pregnant (self or

partner) at any time during the study

16. Have had limb-lengthening or bone-related surgery or expected to have limb-lengthening or bone-related surgery during the study period. Subjects with previous limb-lengthening or bone-related surgery may enroll if surgery occurred at least 18 months prior to the study and healing is complete without sequelae
17. Have had a fracture of the long bones or spine within 6 months prior to screening (except for fracture of digits or toes)
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at least 3x upper limit of normal (ULN) or total bilirubin at least 2x ULN (except for subjects with known history of Gilbert's disease)
19. Evidence of severe sleep apnea requiring surgery or new initiation of CPAP (based on the screening sleep study)
20. Have current malignancy, history of malignancy, or currently under work-up for suspected malignancy
21. Have known hypersensitivity to BMN 111 or its excipients
22. 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
23. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, or would predispose the subject to hypotension (such as recent gastroenteritis or dehydration for any reason)
24. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the PI
25. Have a history of hip surgery or severe hip dysplasia
26. Have a history of clinically significant hip injury in the 30 days prior to screening
27. History of slipped capital femoral epiphysis or avascular necrosis of the femoral head
28. Are unable to lie flat when in prone position (needed for hip monitoring exam)

Additional Exclusion Criteria for Optional, Open-label Extension Phase:

1. Use of restricted therapies during the initial 6 months of the study (see above)
2. Permanently discontinued BMN 111 during the initial 6 months of the study

INVESTIGATIONAL PRODUCT, DOSE, ROUTE, AND REGIMEN:

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, 2 mg, or 10 mg lyophilized, preservative-free, white to yellow powder for reconstitution with sterile water for injection (WFI). The reconstituted solution is colorless to yellow and contains 0.2 mg/mL to 10 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. All reconstitution and dose preparation steps will be performed as indicated in the BMN 111 Injection Guide and Injection DVD.

BMN 111 will be administered in the morning as a single SC injection at the following doses: 2.5 µg/kg, up to 7.5 µg/kg, up to 15.0 µg/kg, and 30 µg/kg.

REFERENCE THERAPY, DOSE, ROUTE, AND REGIMEN:
NA

DURATION OF TREATMENT:
Six months for the initial phase and 18 months for the optional, open-label extension phase, for a total of up to 24 months.

CRITERIA FOR EVALUATION:

Safety: Safety will be evaluated by the incidence of AEs, serious adverse events (SAEs), laboratory test results (urinalysis, chemistry, hematology), changes in vital signs, physical examination, ECG and ECHO results, imaging, clinical hip assessment, and anti-BMN 111 immunogenicity assessments.

Efficacy: Efficacy will be assessed by change from baseline in height growth velocity (annualized to cm/yr), growth parameters, and in body proportions. These 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 and leg, hand and foot. Upper arm to forearm length ratio, upper leg to lower leg length ratio, and upper to lower body segment ratio will be calculated.

Pharmacokinetics

Whenever possible, the following PK parameters will be estimated by non-compartmental analysis:

- Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞)
- Area under the plasma concentration-time curve from 0 to the time of last measurable concentration (AUC0-t)
- C_{max}
- Time to reach C_{max} (T_{max})
- Elimination half-life ($t_{1/2}$)
- Apparent clearance of drug (CL/F)
- Apparent volume of distribution based upon the terminal phase (V_z/F)

The impact of antibodies on PK will be evaluated.

Dose proportionality and drug accumulation after repeat-dose administration will also be evaluated. PK parameters at Day 183 will be compared to Days 1, 10, 29, and 85.

Exploratory:

Biomarkers will be evaluated by change from baseline and may include assessment for cartilage turnover (C-terminal cross-linked telopeptide of type II collagen [CTX-II]), chondrocyte and osteoblast activity (bone-specific alkaline phosphatase [BSAP]), bone formation (pro-collagen Type 1 N-terminal propeptide [P1NP]), osteocalcin; and markers of BMN 111 activity (cyclic guanosine monophosphate [cGMP], N-terminal propeptide of C-type natriuretic peptide [NT-proCNP], and atrial natriuretic peptide [ANP]) as well as additional exploratory biomarkers.

Exploratory imaging assessment data to be evaluated include measurements of the spine, long bones and extremities, as well as measures of growth plate, bone age, and bone mineral density.

Sleep study (conducted at a certified sleep center): A sleep-testing device will be used to assess the

presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring at Screening and on Days 85 and 183 of the initial phase, and Months 12 and 24 of the optional, open-label extension phase. Assessment of sleep apnea will include, but may not be limited to, determining the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index, AHI).

Flexion-extension measures of elbow joint range of motion will be measured with a goniometer.

STATISTICAL METHODS:

Sample Size Determination: Approximately 36 pediatric subjects with ACH will participate in this study. No formal sample size calculations were performed.

Data analysis will be carried out for the initial 6-month period and the extension period, respectively.

Safety Analysis:

For each of the two periods, all subjects who receive at least one dose of study treatment in this study and have any post treatment safety information in the corresponding period will be included in the safety analysis. The safety analysis will be descriptive and will be summarized by dose cohort and all cohorts combined.

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, 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 laboratory tests, vital signs, ECG and concomitant medication data will also be summarized descriptively. Laboratory tests will also be summarized by absolute and percent change from baseline and listed for each dose cohort and for all cohorts combined. Vital signs, ECG and ECHO results will also be listed.

Efficacy Analysis:

Efficacy analysis will be carried out for the initial 6-month period and the extension period. For each of the two periods, data from all subjects who receive at least one dose of study treatment and who have post treatment data for any efficacy endpoint in the corresponding period will be included in the efficacy analysis for that endpoint.

Annualized growth velocity, based on standing height measures at every 6-month time point, will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum). The test of hypothesis of no change from the baseline in growth velocity will be conducted via paired t-test for the initial 6-month period and p-value will be considered descriptive. Changes in body proportion ratios (upper arm to forearm length ratio, upper leg to lower leg length ratio, and upper to lower body segment ratio) from baseline to each scheduled time point will be similarly summarized and tested at the initial 6-month time point. The measurement of standing height will be converted to age-and sex-appropriate standard score (SDS), also referred to as Z-score, by comparison with normal reference standards (not ACH). The Z-score will be summarized similarly to growth velocity. Results will be summarized by dose cohort and for all cohorts combined.

Other anthropometric measures (sitting height, weight, head circumference, upper and lower arm and leg, hand and foot, etc.) will be summarized at each time point and will be evaluated for changes from baseline.

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4 LIST OF ABBREVATIONS AND DEFINITIONS OF TERMS

µg/kg	microgram/kilogram
ACE	angiotensin-converting enzyme
Ach	$Fgfr3^{G380R}$ achondroplasia mouse model
ACH	achondroplasia
AE	adverse event
AHI	apnea hypopnea index
ALT	alanine aminotransaminase
ANP	atrial natriuretic peptide
AP	anterior-posterior
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMD	bone mineral density
BMI	body mass index
BNP	B-type Natriuretic Peptide
BP	blood pressure
BSAP	bone-specific alkaline phosphatase
°C	degree Celsius
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
C_{max}	maximum observed plasma concentration
CNP	C-type natriuretic peptide
CNP53	C-type natriuretic peptide (53 amino acids in length)
CRA	clinical research associate
CRF	case report form
CT	X-ray computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTX-II	C-terminal cross-linked telopeptide of type II collagen
CV	cardiovascular
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
FDA	Food and Drug Administration
FGF	fibroblast growth factor

G380R	substitution in the transmembrane domain of the FGFR3 receptor at position 380
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IgE	immunoglobulin E
IP	investigational product
IRB	institutional review board
kDa	kilodalton
LV	left ventricular
MAPK	mitogen-activated protein kinase
mg	milligram
mL	milliliter
mm Hg	millimeters of mercury
msec	millisecond
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibodies
NEP	neutral endopeptidase
NOAEL	no observed adverse effect level
NP	natriuretic peptide
NPR-B	natriuretic peptide receptor type B
NT-proCNP	N-terminal propeptide of C-type natriuretic peptide
P1NP	pro-collagen Type 1 N-terminal propeptide
PA	posterior-anterior
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
PR	a measure of time between the start of the P wave to the start of the QRS complex
QCT	quantitative computed tomography
QRS	deflection observed on an ECG that corresponds to the depolarization of the right and left ventricles
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
SC	subcutaneous
SCFE	slipped capital femoral epiphysis

SD	standard deviation
$t_{1/2}$	elimination half-life
TAb	total antibody
TD	thanatophoric dysplasia
TEAE	treatment-emergent adverse event (an AE which occurs post-dose or which is present pre-dose and becomes more severe post-dose)
T_{max}	time to reach C_{max}
ULN	upper limit of normal
WFI	water for injection

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 Ethics Committees (ECs) 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 assuring prompt resolution of any queries.

Prior to initiating the study, the Investigator will obtain written confirmation that the institutional review board (IRB) or independent ethics committee (EC) 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/EC will be provided to BioMarin or its designee. The Investigator will provide the IRB/EC with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information or educational materials provided to the subjects, including all ICFs translated to a language other than the native language of the clinical site. The study will not be initiated and Investigational Product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/EC 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/EC 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, including 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:

- US 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 (ICH E6)
- The ethical principles established by the Declaration of Helsinki

Specifically, this study is based on adequately performed laboratory and animal experimentation, and a human clinical trial in healthy volunteers. The study will be conducted under a protocol reviewed and approved by an IRB/EC 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 ICF, in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), United States (US) 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/EC approval. BioMarin and the IRB/EC 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 18 years will provide written assent (if required by local regulations or the IRB/EC), 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 subjects) and will maintain the original in the record file of the subject.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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.

Prior to beginning the study, the Investigator at each site must provide to BioMarin or designee, a fully executed and signed 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 Regulatory Affairs Department (or designee) will be responsible for the timely reporting of SAEs to appropriate regulatory authorities as required.

A Coordinating Investigator will be identified who will be responsible for study overview. 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.

Laboratory evaluations will be performed at central laboratories unless use of a local laboratory is clinically indicated in order to have expedited results. See Laboratory Manual for detailed requirements.

7 INTRODUCTION

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

ACH is a rare disease with a prevalence of 1/25000 in the US (Wynn, 2007, Am J Med Genet A). It is a chondrodysplasia characterized by rhizomelic short limbs and short stature. The adult height is just over 4 feet. 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 are no approved pharmacologic interventions for ACH. Human Growth Hormone (Genotropin®, Humotrope®, and Nutropin®) is not approved for ACH as no long-term effects on growth were demonstrated in the ACH population. Current treatments 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, J Am Acad Orthop.Surg.); (Horton, 2007, Lancet).

ACH is caused by a gain-of-function mutation in FGFR3, 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 with normal stature. Other skeletal chondrodysplasia are caused by gain-of-function mutation in FGFR3. Their phenotypes are similar to ACH but their severities vary from mild (hypochondroplasia) to lethal (TD), depending on the genetic mutation.

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, Hum.Mutat.). 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, J.Cell Sci.); (Yasoda, 2004, Nat.Med.); (Yasoda, 2009, Endocrinology); (Pejchalova, 2007, Mol.Genet.Metab). This crosstalk was demonstrated in a mouse model of FGFR3-related chondrodysplasia (Yasoda, 2004, Nat.Med.); (Yasoda, 2009, Endocrinology). The dwarfism

phenotype of mice harboring the FGFR3^{G380R} mutation was rescued by expression of 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, J Biotechnol). BMN 111 was designed to 1) mimic CNP activities in terms of receptor binding and pharmacological activity and 2) be resistant to 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, J.Pharmacol.Exp.Ther.).

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

7.1 Nonclinical Studies

The nonclinical studies characterized the primary pharmacodynamic activity of BMN 111 in normal mice, rats and cynomolgus monkeys and in two mouse models of ACH (TD [severe] and Ach [mild]). Respiratory and CNS safety pharmacology were evaluated in rats and CV safety pharmacology in telemeterized monkeys. Repeat-dose toxicity and TK GLP studies were completed including two 28-day studies: one in the young adult rat and one in the juvenile monkey, three 26-week studies: one in the juvenile rat, one in the adult rat and one in the juvenile monkey, and one 44-week study in sexually mature cynomolgus monkeys (with open growth plates).

Overall, BMN 111-related findings were limited to the known mechanism of action of CNP on the growth plate and vasculature, resulting in the promotion of longitudinal bone growth at hemodynamically tolerated dose levels. Additionally, 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 BMN111-treated rats and monkeys compared to the vehicle control. There were no BMN 111-related effects on respiratory, CNS, or sexual development and reproductive performance. Adverse skeletal changes associated with exaggerated growth were seen in all normal nonclinical species with open growth plates, and were dose-, exposure- and time-dependent. These effects included abnormally shaped femoral head, acetabular growth center/plate dysplasia and concomitant articular cartilage degeneration with clinical manifestations of restricted use of hips. [redacted]

7.2 Previous Clinical Studies

Study 111-202 is the second study of BMN 111 in humans. Study 111-101 (A Phase 1, 2-Part, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Subcutaneous Doses of BMN 111 Administered to Healthy Adult Volunteers) was the first-in-human study of BMN 111.

Results from Study 111-101 initially informed Study 111-202. [redacted]

7.3 Study Rationale

Study 111-202 is designed as a proof-of-concept study for BMN 111 in children with ACH. The initial phase of this study is 6 months and will allow for assessment of the effect of daily BMN 111 administration on safety, tolerability, growth velocity, absolute growth, and body proportions at doses ranging from 2.5-30 µg/kg given subcutaneously daily. A clinically relevant increase in annualized growth velocity is considered to be in the range of 25%-50% change from baseline, although the targeted increase may be refined based on ongoing comprehensive safety and efficacy review of BMN 111. Additional exploratory endpoints that reflect the medical complications of ACH will also be evaluated.

BMN 111 drug exposure, BMN 111 pharmacodynamics (PD; i.e., biomarkers), and the relationship of BMN 111 and immunogenicity will be explored, as will changes in BMI, growth plate morphology, long-bone growth, lumbar spine morphology, and sleep apnea.

After completing the initial phase of the study lasting 6 months, subjects may enroll in an optional, open-label extension period of approximately 18 months to commence at the end of the initial phase of the study, making a total study duration of approximately 25 months, including a 1-month safety follow-up visit. The rationale for the extension phase is to assess the long-term safety and tolerability of BMN 111 in children with ACH; and to assess longer-term effects of BMN 111 on growth in these children.

Study durations of 2 years and longer have been previously reported in studies of growth hormone in children with ACH (Stamoyannou, 1997, Am J Med Genet), (Tanaka, 1998, Eur J Endocrinol.).

The Cohort 4 dose of 30 µg/kg was selected with the intent to achieve exposures expected to result in further increases in growth velocity in children with ACH with an acceptable safety profile.

PK data from Study 111-202 indicate that exposures achieved in ACH children given 15 µg/kg are comparable to a minimally biologically active exposure range but less than those required for significant growth in monkeys. PK data support evaluation of doses of 30 µg/kg to further characterize dose-response relationships and potentially achieve exposures resulting in further growth.

Safety data in monkeys support dosing ACH children at the proposed doses of 30 µg/kg daily, with careful monitoring and management of hemodynamic and skeletal changes.

To date, clinical data in Study 111-202 demonstrated that BMN 111 was generally well tolerated at doses up to 30 µg/kg without evidence of abnormal growth or significant cardiovascular effects.

7.4 Summary of Overall Risks and Benefits

7.4.1 Summary of Risks from Nonclinical Studies

7.4.2 Summary of Risks from Clinical Studies

7.4.2.1 111-101

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.

7.4.2.2 111-202

Based on review of this ongoing phase 2 clinical trial, injection site reactions have been identified as risks associated with BMN 111 injections. Hypotension and hypersensitivity reactions are potential risks associated with BMN 111 injections. For a detailed summary of risks, please refer to the current IB.

In the phase 2 study BMN 111-202, injection site reactions were the most common AEs reported and are considered as an identified risk associated with BMN 111 injections. The most common injection site reactions across all cohorts included: injection site erythema, injection site swelling, and injection site urticaria. Of note, all injection site reactions have been reported as non-serious and grade 1 in severity, and no subjects have discontinued from the study or permanently discontinued study treatment as a result of the events.

The most important potential risks identified to date include hypotension (and complications related to hypotension and/or tachycardia) and the development of anti-BMN 111 antibodies. Anti-BMN 111 antibodies have the potential to mediate allergic reactions, reduce efficacy, and/or cross-react with endogenous CNP or other undefined agents. Anti-BMN 111 antibodies continue to be monitored in the study. No grade 2 or higher or serious hypersensitivity reactions have been reported to date. Reported adverse events of hypotension have been mild, non-serious, and have resolved without medical intervention. Both these potential risks will continue to be closely monitored.

7.4.3 Summary of Potential Benefits from Clinical Studies

For children who receive BMN 111 as part of this study, potential benefits may include improvement of annualized growth velocity rates; and improvement of the disproportionate growth with potential benefits on several of the medical complications of ACH (lumbar spine angulation, tibial bowing, and sleep apnea).

8 STUDY OBJECTIVES

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

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

The primary objective of the study extension is:

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

The secondary objectives of the study are:

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

The exploratory objectives of the study are:

- To evaluate change from baseline in QCT bone mineral density (BMD) following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate changes from baseline in growth plate morphology following daily SC injections of BMN 111 for 6 months, and up to 24 months
- To evaluate changes from baseline in long-bone growth, and morphology of the spine following daily SC injections of BMN 111 administered for 6 months, and up to 24 months
- To evaluate changes from baseline in sleep apnea following daily SC injections administered for 6 months, and up to 24 months
- To evaluate changes from baseline in elbow joint range of motion by goniometry, following daily SC injections administered for 6 months, and up to 24 months
- To evaluate changes from baseline in BMN 111 activity biomarkers and bone/collagen biomarkers following daily SC injections of BMN 111 administered for 6 months, and up to 24 months

- To evaluate immunogenicity from baseline and assess impact on safety, PK, and efficacy measures following daily SC injections of BMN 111 during the 6 months, and up to 24 months

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

Study 111-202 is a pediatric, Phase 2, open-label dose-escalation study of approximately 36 subjects with a clinical diagnosis of ACH. Subjects who are 5 to 14 years old inclusive, with documented ACH confirmed by genetic testing, have at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry, and who meet the study eligibility criteria will participate. BMN 111 will be administered daily for 6 months, provided none of the protocol-defined stopping or safety criteria, defined below, are met. On days of scheduled clinic visits, BMN 111 administration will be performed in the clinic relative to the scheduled assessments and procedures defined in the 111-202 Schedule of Events (Table 9.1.1).

Comprehensive outpatient safety monitoring will be conducted for all subjects over the course of the first 10 days after the first dose of study drug is received, followed by close monitoring throughout the duration of the study. The comprehensive safety monitoring includes a minimum of 8 hours post-dose observation on the first two days of dosing and at least 4 hours post dose observation on study Days 3 and 4. Subjects may be observed for a longer duration and/or additional visits may be added for further safety assessment on Days 5-9 at the discretion of the Investigator in consultation with the BioMarin Medical Monitor. A visit on Day 10 concludes the comprehensive outpatient safety-monitoring period. Vital signs will be monitored frequently during the initial period of Days 1-10, including approximately every 10-20 minutes for the first 2 hours post dose on visit days. Additional safety assessments during this period are ECG, physical exams, AE assessment, and clinical labs (Table 9.1.1).

A maximum of five children from one gender may be enrolled in each cohort if the total size of the cohort is eight or nine subjects; a maximum of six children from one gender can be enrolled in each cohort if the size of the cohort is 10 subjects.

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

- Cohort 1 (n=8): daily morning dose of 2.5 µg/kg BMN 111
- Cohort 2 (n=8): daily morning dose of up to 7.5 µg/kg BMN 111
- Cohort 3 (n=8-10): daily morning dose of up to 15.0 µg/kg BMN 111
- Cohort 4 (n=8-10): daily morning dose of 30.0 µg/kg BMN 111

It is generally expected that after subjects are tolerating the drug well and specified criteria have been met, caregivers will begin administering study drug. In the initial phase, on weeks when caregivers/subjects will not see either a home healthcare professional or a study staff member, a phone call by the study staff member to the caregiver/subject will be required. During the call, study staff will ask the caregiver about correct administration procedures, assess adverse events (AEs), record concomitant medications, and answer questions. During the optional, open-label extension phase, the call frequency will change to every 2 weeks (± 3 days) for the first 6 months of the extension phase and monthly (± 5 days) thereafter. A follow-up phone call will take place 7-10 days after dose adjustment visits.

Dose Escalation Plan during the Initial 6 Months of the Study

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

Subjects will remain on a fixed daily dose throughout the initial 6-month treatment period. Subjects in each cohort continue to receive daily dosing (Cohort 1, 2.5 µg/kg; Cohort 2, up to 7.5 µg/kg, Cohort 3, up to 15 µg/kg, and Cohort 4, 30.0 µg/kg) for 6 months unless stopping criteria are met. If stopping criteria are not met after all 8-10 subjects in a cohort have completed their first 10 days of cohort dosing, and after DMC review and approval, the subsequent cohort may be open to enrollment.

Optional, Open-label Extension Phase of the Study

In the open-label, optional extension phase, the long-term safety, tolerability, and effects of BMN 111 on growth will be evaluated in children with ACH who have completed an initial 6 months of treatment with BMN 111. At the Day 183/6-month visit, subjects who elect to continue participating in the optional open-label extension phase will be consented for the extension phase. These subjects will receive study drug on Day 184 of the initial phase, which also marks the beginning of the extension phase. Drug treatment will continue without interruption. Subjects who decline to participate in the extension phase will return at Day 208 for the Safety Follow-Up visit and exit the study.

In the 18-month optional, open-label extension phase, subjects within each cohort will either remain on the same stable dose that they have been receiving during the initial 6 months of treatment, or the dose for all subjects in the cohort (except cohort 4) may be increased based on the following rules:

(1) Initial dose was determined to exhibit suboptimal efficacy on the basis of growth measurements after at least 6 months of treatment based on the review of the data for all subjects in the cohort.

(2) Initial dose, and other doses higher than the initial dose, but lower than the dose to which the cohort is being increased were generally well tolerated for at least 6 month based on review of data for all subjects in the cohort.

(3) The dose to which the subjects in the cohort are being escalated has been previously shown to be well tolerated for at least 10 days of comprehensive outpatient safety monitoring as described in Section 9.1, based on DMC review of the data for all subjects in the cohort previously assigned to the considered dose.

During the optional, open-label extension phase, visits will take place at 2- to 3-month intervals. The site will call the caregiver/subject between the visits every two weeks for the first 6 months and every month for the remainder of the study.

DMC data review will occur approximately every 4 months during the optional, open-label extension phase.

Subjects who participate in the open-label extension phase of study 111-202 will have the option to enroll in the long-term extension study 111-205 at the Month 24/Study Completion Visit. Month 24 assessments will serve as Baseline/screening assessments for entry to study 111-205.

Criteria for Dose Adjustment Visits

The timing of dose adjustments and follow-up visits after adjustment is contingent upon the time at which the dose adjustment was recommended. One of two scenarios will apply:

- Scenario 1: Recommendation to adjust the dose is made when the next scheduled visit is ≤4 weeks away from the date that the dose change is communicated to sites. Dose adjustment will be done at the next scheduled visit.
- Scenario 2: Recommendation to adjust the dose is made when the next scheduled visit is >4 weeks away from the date that the dose change is communicated to sites. An unscheduled dose adjustment visit will be done within 4 weeks.

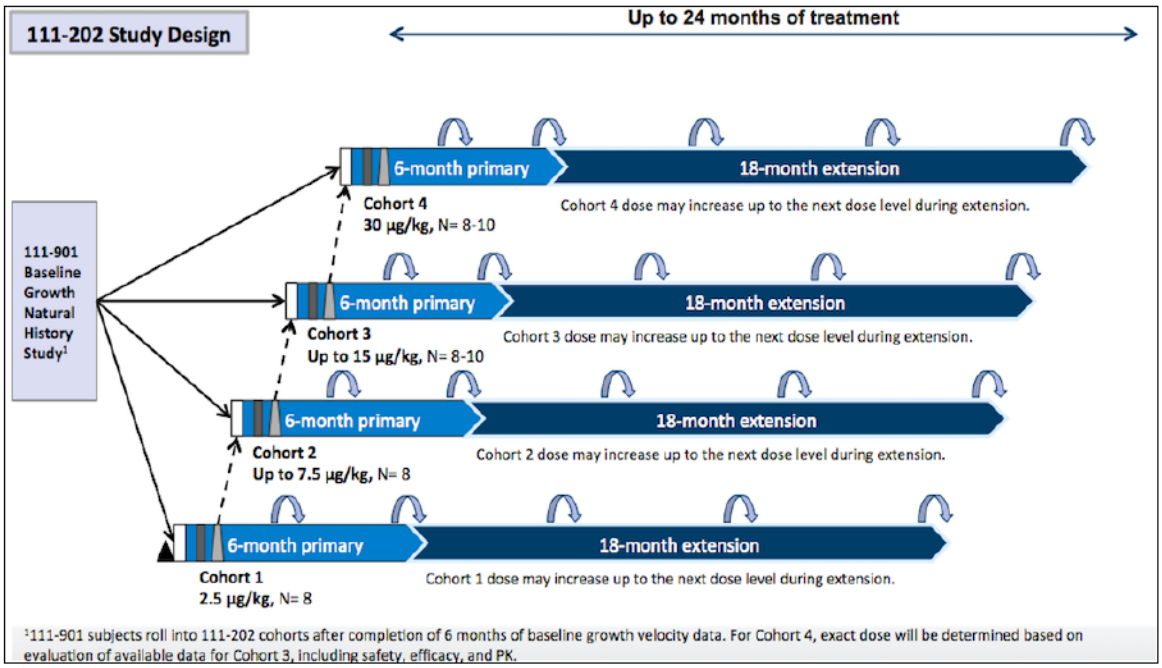
In both cases, a follow-up visit 4 weeks (± 2 weeks) is required after the dose adjustment. The dose adjustment follow-up visit will be scheduled 4 weeks after the dose adjustment visit UNLESS a regularly scheduled visit occurs within the ± 2-week visit window, in which case a separate follow-up visit will not be required.

Please refer to Table 9.1.3 for a list of assessments associated with Dose Adjustment and Follow-up Visits.

Assessments

For a discussion of efficacy assessments, see Section 9.10.2; exploratory efficacy assessments, Section 9.10.3; safety assessments, Section 9.10.4; and PK/PD variables, Sections 9.10.2.1 and 9.10.3.1. The 111-202 study design is presented in Figure 9.1.1.

Figure 9.1.1: 111-202 Study Design



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

Table 9.1.1: Schedule of Events for 6-Month Initial Phase of the Study

Procedure[a]	Screening Day -30 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 10 ± 1 Day	Day 15 ± 1 Day	Day 22 ±1 Day	Day 29 ±1 Day	Day 43 ±7 Days	Day 85 ± 7 Days	Day 127 ±7 Days	Day 183±7 Days M6	Safety Follow-up Day 208 ±7 Days	Early Term
Informed consent	X												X		
Medical history[b]	X														
Parental height[c]	X[c]														
Genetic testing (if needed)[d]	X														
Physical examination[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tanner Stage of Pubertal Development	X												X		X
Pregnancy test[e]	X									X	X	X	X	X	X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anthropometric measurements[g]	X									X	X	X	X		X[g]
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Elbow joint range of motion[h]	X									X	X	X	X	X	X
Baseline hip assessment, including AP x-ray of pelvis[i]	X														
Hip monitoring (refer to guidance)[j]													X		X
Sleep apnea assessments[k]	X										X		X		X
ECG	X					X			X		X		X	X	X
ECHO	X												X		
Clinical labs	X	X			X	X	X		X	X	X	X	X	X	X

Procedure[a]	Screening Day -30 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 10 ± 1 Day	Day 15 ± 1 Day	Day 22 ±1 Day	Day 29 ±1 Day	Day 43 ±7 Days	Day 85 ± 7 Days	Day 127 ±7 Days	Day 183±7 Days M6	Safety Follow-up Day 208 ±7 Days	Early Term
(hematology, chemistry, and urinalysis)[l]															
Urine chemistry[m]	X	X				X	X	X	X	X	X	X	X	X	X
Thyroid function tests	X												X		
Serum glucose levels	X												X		
Vitamin D	X												X		X
Anti-BMN 111 immunogenicity[n]		X				X			X		X		X	X	X
PD BMN 111 activity biomarkers[o]	X	X				X	X		X	X	X	X	X		X
NTproCNP (plasma)	X								X	X		X	X		X
ANP (plasma)		X				X			X			X			
cGMP (urine)		X				X	X		X	X	X	X	X		
PD bone and collagen biomarkers[p]	X	X				X	X	X	X	X	X	X	X		X
BSAP (serum)	X	X				X	X		X	X	X	X	X		X
P1NP (serum)	X	X					X		X	X	X	X	X		X
CTX-II (urine)	X	X					X	X	X	X	X	X	X		X
Osteocalcin (serum)	X												X		X
PK[q]		X				X			X		X		X		
Quantitative computed tomography (QCT) of forearm and tibia[s,v]	X												X		

Procedure[a]	Screening Day -30 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 10 ± 1 Day	Day 15 ± 1 Day	Day 22 ±1 Day	Day 29 ±1 Day	Day 43 ±7 Days	Day 85 ± 7 Days	Day 127 ±7 Days	Day 183±7 Days M6	Safety Follow-up Day 208 ±7 Days	Early Term
Bone age x-ray (PA of hand and wrist)[t,v]	X												X		X[q]
AP lower extremity x-ray[u,v]	X												X		X
Lateral lumbar spine x-ray[w]	X												X		
AP x-ray of spine[x]	X														
Concomitant medications[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X		
Study drug accountability		X	X	X	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	X	X	X
Weekly phone calls or home health visits[bb]	Only required on weeks when there are no study visits.														

Table 9.1.2: Optional, Open-label Extension Phase of the Study

Procedure[a]	M8 ± 7 Days	M10 ± 7 Days	M12 ± 7 Days	M15 ± 14 Days	M18 ± 14 Days	M21 ± 14 Days	M24/Study Completion Visit[z] ± 14 Days	Safety Follow-up[aa] M25 ± 7 Days	Early Term
Physical examination[e]	X	X	X	X	X	X	X	X	X
Tanner Stage of Pubertal Development			X		X		X		X
Pregnancy test[e]	X	X	X	X	X	X	X	X	X
Vital signs[f]	X	X	X	X	X	X	X	X	X
Anthropometric measurements[g]	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Elbow joint range of motion[h]	X	X	X	X	X	X	X	X	X
Hip monitoring (refer to guidance)[j]			X		X		X		X
Sleep apnea assessments[k]			X				X		X[k]
ECG	X	X	X	X	X	X	X		X
ECHO			X		X		X		X
Clinical labs (hematology, chemistry, and urinalysis)[l]	X	X	X	X	X	X	X	X	X
Thyroid function tests							X		
Urine chemistry[m]	X	X	X	X	X	X	X	X	X
Vitamin D							X		X
Anti-BMN 111 immunogenicity[n]	X	X	X	X	X	X	X	X	X
PD BMN 111 activity biomarkers[o]			X		X		X		X
NTproCNP (plasma)			X				X		X
ANP (plasma)			X				X		

Procedure[a]	M8 ± 7 Days	M10 ± 7 Days	M12 ± 7 Days	M15 ± 14 Days	M18 ± 14 Days	M21 ± 14 Days	M24/Study Completion Visit[z] ± 14 Days	Safety Follow-up[aa] M25 ± 7 Days	Early Term
cGMP (urine)			X		X		X		
PD bone and collagen biomarkers[p]	X	X	X	X	X	X	X		X
BSAP (serum)	X	X	X	X	X	X	X		X
P1NP (serum)	X	X	X	X	X	X	X		X
CTX-II (urine)	X	X	X	X	X	X	X		X
Osteocalcin (serum)			X				X		X
PK[q,r]	X	X	X	X	X	X	X		
Quantitative computed tomography (QCT) of forearm and tibia[s,v]			X				X		X
Bone age x-ray (PA of hand and wrist)[t,v]			X		X		X		X
AP lower extremity xray[u,v]			X				X		X
Lateral lumbar spine x-ray[w]							X		X
AP x-ray of spine[x]							X		X[x]
Concomitant medications[y]	X	X	X	X	X	X	X	X	X
Study drug administration	X	X	X	X	X	X	X		
Study drug accountability	X	X	X	X	X	X	X		X
Adverse events[aa]	X	X	X	X	X	X	X	X	X
Phone calls[bb]	Every two weeks (± 3 days) for the first 6 months and every month (± 5 days) for the remainder of the study.								

NOTE: ALL ASSESSMENTS PRE-DOSE EXCEPT WHEN SPECIFIED.

[a] Day 10-29 visits have a ± 1-day window; Days 43-183 visits have a ±7 Day window; there is no Day 0. Months 8-12 have a ± 7-day window. Months 15-24 have a ± 14-day window. Measurement and imaging assessments can be conducted either pre-dose or post-dose.

[b] Medical history, including growth history and ACH-related 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.

[c] Standing height of the participant's biological parents will be assessed. 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 biological parent is not available during the course of the study to take their standing height, if consented, can provide their stated height.

[d] 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 the 111-202 study include the identification of FGFR3 mutation (G346E, G375C, G380R, or "other") OR a lab certification with the study specific mutation documented.

[e] Complete physical exam includes all major body systems, including assessment of general appearance; CV; dermatologic; head, eyes, ears, nose, and throat; lymphatic; respiratory; gastrointestinal (GI); musculoskeletal; and neurological/psychological and genitourinary. 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 to confirm pregnancy.

[f] All treatment visits have pre-dose vital sign assessments. Vital signs at pre-dose include: body temperature in degrees Celsius (°C), heart rate, BP, and respiratory rate. Post-dose measurements include heart rate and BP.

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.			
	Assessment Frequency			
Dosing Visits	0-1 hr post-dose	0-2 hr post-dose	2-4 hr post dose	4-8 hr post-dose
Days 1, 2		q 15 min (± 5 min)	q 30 min (± 5 min)	q 60 min (± 10 min)
Days 3, 4 and dose adjustment visit in optional, open-label extension phase		q 15 min (± 5 min)	q 30 min (± 5 min)	
All other dosing visits	q 15 min (± 5 min); final assessment prior to end of visit (if longer than 1 hr)			

1. Vital sign measurements are taken once per timepoint in a sitting position after at least 5 minutes of rest.
2. Left brachial arm should be the first method of assessment considered, and the same site should be used for measurement of BP in each subject throughout the study.
3. Heart rate should be taken at each timepoint that BP is measured.
4. 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.
5. 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.
6. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
7. If a subject has a hypotensive event (or 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 patient as defined by PI) and symptoms (if present) resolve.

[g] Growth measures may be collected approximately the same time each day (± 2 hr around the time when the first measurement assessment was taken at Screening). Measurements may include but are not limited to standing height, sitting height, weight, head circumference, upper and lower arm and leg, hand and foot. Measurements not taken in the midsagittal plane should be taken on the right side of the body when possible. Take anthropometric measurements at early termination visit only if subject discontinues after Day 43.

[h] The same elbow will be used each time the measurement is taken.

[i] If subject is already enrolled, baseline hip assessment, including x-ray of pelvis, will be conducted at next scheduled visit. If this visit overlaps with a scheduled hip-monitoring visit, the hip assessment will be conducted.

[j] Hip monitoring: this assessment will include medical history of the hip and physical exam to determine changes in hip function or pain with hip range of motion. Changes from baseline will trigger further evaluation.

[k] If sleep apnea reading is not accurate, subject may need to repeat assessment. Sleep apnea assessment at early termination visit only if subject discontinues after 18 months.

[l] Clinical labs (hematology, chemistry, and urinalysis) are all pre-dose draws (samples can be drawn anytime during the visit if there is no drug administration).

[m] First void upon arrival at the clinic. Screening, Days 1, 10, 15, 22, 29, 43, 85, 127, 183, M8, M10, M12, M15, M18, M21, M24, follow-up 4 wk post-escalation dose, safety follow-up, and early termination. One hr, 2 hr, and 4 hr post-dose collected Days 1, 10, 15, 29, 43, 85, 127, 183, M12, M18, M24 (± 20 minutes for all urine sample time points).

[n] Antibodies: Total and neutralizing anti-BMN 111 immunogenicity samples (serum) will be drawn pre-dose at each time point listed on the SOE. Total immunoglobulin E (IgE) and drug-specific IgE will be drawn on Day 1 and in the event of significant hypersensitivity adverse event (as defined in Section 9.10.4.4.6.2), or at Investigator or Sponsor discretion. The drug-specific IgE sample should be drawn at least 8 hr after the event start time and before the next dose. A sample for total IgE and serum tryptase should be drawn within an hour of the start of the event when possible or during the unscheduled safety visit.

[o] NTproCNP: Screening; at dosing visits, plasma pre-dose and 4 hr post-dose (± 30 minutes); ANP: plasma pre-dose, 15 min post-dose (± 5 minutes), and 2 hr post-dose (± 15 minutes); cGMP: urine pre-dose, 1 hr post-dose, 2 hr post-dose, and 4 hr post-dose (± 20 minutes for all urine sample time points).

[p] All bone and collagen biomarkers are drawn pre-dose (samples can be drawn anytime during the visit if there is no drug administration).

[q] For subjects in the 6-month initial phase, on Days 1, 10, 29, 85, and 183, PK samples are collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 60 (± 5 min), 90 (± 5 min), 120 (± 5 min), and 180 (± 5 min) minutes post dose. For subjects on a fixed dose in the optional, open-label extension phase, full PK samples will be taken at Months 12 and 24. Partial PK samples will be taken at four time points (pre-dose, 15, 30, and 60 minutes post dose) to estimate exposure and to correspond with immunogenicity assessments. These partial PK draws will take place at Months 8, 10, 15, 18, and 21 with immunogenicity assessments (samples can be drawn anytime during the visit if there is no drug administration).

[r] For subjects whose doses are adjusted upward in the optional, open-label extension phase, full PK samples will be drawn on Day 1 of dose adjustment and at subsequent visits per collection schedule in Table 9.10.2.1.1. Partial PK samples will also be drawn at subsequent visits per collection schedule in Table 9.10.2.1.1.

[s] For measurement of growth plate, BMD, bone length. This scan will be acquired with a standard CT scanner, calibration phantom, and designated software, using a predetermined low radiation dose protocol, which avoids direct radiation to the head and torso.

[t] Bone age x-ray and AP lower extremity (in the initial phase of the study) are obtained at the early termination visit only if subject discontinues after Day 60 (to reduce unnecessary radiation exposure).

[u] For AP lower extremity x-ray, assess the same side of the body throughout the study.

[v] QCT, bone age, and lower extremity (in the optional, open-label extension phase of the study) are obtained at the early termination visit only if the previous assessment was done more than 60 days prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC).

[w] Lateral lumber spine x-ray at early termination visit only if subject discontinues after 18 months.

[x] AP x-ray of spine at early termination visit only if subject discontinues after 18 months.

[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] Subjects who participate in the open-label extension phase of study 111-202 will have the option to enroll in the long-term extension study 111-205 at the M24/Study Completion Visit. Month 24 assessments will serve as Baseline/screening assessments for entry to study 111-205.

[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. If a subject is discontinued from the study prematurely, AEs and SAEs will be recorded at the Early Termination visit. The Day 208 Safety Follow-up visit is not required if a subject enrolls in the optional, open-label extension study at the Day 183/Month 6 visit. The Month 25 Safety Follow-up visit will be waived if a subject enrolls in the 111-205 extension study at the Month 24/Study Completion visit.

[bb] In the initial phase of the study, on weeks when caregivers/subjects will not see either a home healthcare professional or a study staff member, a phone call by the study staff member to the caregiver/subject will be required. During the call study staff will ask the caregiver about correct administration procedures, assess adverse events (AEs), record concomitant medications, and answer questions. During the optional, open-label extension phase, the call frequency will change to every 2 weeks (± 3 days) for the first 6 months of the extension phase and monthly (± 5 days) thereafter.

Table 9.1.3: Criteria for Dose Adjustment Visits

Dose Adjustment Recommendation*	Dose Adjustment Made	Dose Adjustment Visit Procedures	Follow-up Phone call	4-week Follow-up Visit (± 2 weeks)	Procedures Done at Follow-up Visit
Next scheduled visit is ≤4 weeks away	At next scheduled visit	The procedures below are done at dose adjustment visits. If the dose adjustment visit happens at a regularly scheduled visit, conduct the remaining scheduled visit procedures as well.	7-10 days post dose adjustment	Schedule 4 weeks after the dose adjustment visit if a regularly scheduled visit does not occur within the visit window	The procedures below are done at adjustment follow-up visits. If the adjustment follow-up visit happens at a regularly scheduled visit, conduct the remaining scheduled visit procedures as well.
Next scheduled visit is >4 weeks away	Unscheduled dose adjustment visit to be done within 4 weeks from DMC decision to dose adjust	• Physical exam • Vital signs • Weight • Anthropometry • ECG • Clinical labs • Urine chemistry • Full PK • Concomitant medications • Drug administration • Drug accountability • AEs			• Physical exam • Vital signs • Weight • Clinical labs • ECG • Concomitant medications • Drug administration • Drug accountability • AEs

* If a dose is de-escalated, study staff will request that the subject come in as soon as possible. Follow-up occurs 4 weeks later.

9.1.1 Dose Modifications for Safety

9.1.1.1 Stopping Criteria

Individual Subject Stopping Criteria

For individual subjects, temporary dosing suspension, permanent discontinuation of dosing, or, in exceptional circumstances, dose reduction will be considered and DMC will be informed (at a minimum) if any of the following occur:

- Any TEAE at least Grade 3 assessed by the Investigator and/or Sponsor Medical Monitor
- Any two TEAEs Grade 2 experienced by the same subject within 1 week including two symptomatic hypotension events within 1 week (non-urgent medical intervention indicated) or any Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Prolongation of QTc-F interval to more than 500 msec, ventricular tachycardia greater than five beats
- Any clinically significant worsening of existing disproportionate growth, as determined by physical measurement ratios and/or Investigator assessment based on imaging, measurement or clinical observation findings
    - Upper arm to forearm length ratio
    - Upper leg to lower leg length ratio
    - Upper to lower body segment ratio
- Clinically significant worsening of bone morphology as evidenced by development of tibial bowing, or worsening of existing tibial bowing as observed via clinical or radiographic assessment
- Clinically significant worsening of elbow joint range of motion based on clinical assessment and on goniometry measurements of flexion-extension
- Findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as decided by principal investigator and in consultation with sponsor medical monitor and orthopedic specialist (if needed)

If the subject meets any stopping criteria, after Investigator consultation with the BioMarin Medical Monitor and DMC (if warranted), the subject may be re-challenged at the same dose. If the subject meets stopping criteria on re-challenge or if re-challenge at same dose is not clinically indicated, other options that may be considered include:

- Re-challenge at lower dose with consideration given to upward titration to tolerated dose/cohort dose
- Permanent treatment discontinuation (with and option of ongoing assessment in the study)

Cohort Stopping Criteria

For an open cohort and all higher dose cohorts, temporary dosing suspension or dose reduction will be considered and DMC review will be conducted (at a minimum) if any of the following occur:

- Any two subjects within a cohort have TEAE at least Grade 3; any two subjects have two symptomatic hypotension events within 1 week each Grade 2 (non-urgent medical intervention indicated); or any two subjects have a Grade 3 hypotension event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor Medical Monitor
- Any one subject with any TEAEs Grade 4 or 5 assessed by the Investigator and/or Sponsor Medical Monitor
- Any two subjects within a cohort have prolongation of QTc-F interval to more than 500 msec, ventricular tachycardia greater than five beats
- Any two subjects within a cohort have clinically significant worsening of existing disproportionate growth, as determined by physical measurement ratios and/or Investigator assessment based on imaging, measurement or clinical observation findings
    - Upper arm to forearm length ratio
    - Upper leg to lower leg length ratio
    - Upper to lower body segment ratio
- Any two subjects within a cohort exhibit clinically significant worsening of bone morphology as evidenced by development of tibial bowing, or worsening of existing tibial bowing as observed via clinical or radiographic assessment
- Any two subjects exhibit clinically significant worsening of elbow joint range of motion based on clinical assessment and on goniometry measurements of flexion-extension
- Any two subjects exhibit findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as decided by principal investigator and, if needed, in consultation with sponsor medical monitor and orthopedic specialist (if needed)
- Any other reason DMC advises temporary discontinuation of cohort dosing until further review of safety data is conducted

Sites have 1 business day to report to BioMarin an event that meets individual or cohort stopping criteria. DMC can ask for additional available data while reviewing subject(s) who met individual stopping criteria, or subjects with any other new safety finding. In order to assess significance of the findings, DMC can request to review additional data for other subjects in the cohort, or any other subjects in the study. These additional data include, but are not limited to, physical exam, vital signs, anthropometric measures, ECG, ECHO, and lab results. The DMC will review available, relevant safety data within 5-7 days after BioMarin is apprised of an event. BioMarin will keep all sites informed of enrollment pauses, to ensure that no subjects in the cohort (and all higher cohorts) that are affected by stopping criteria are treated, and no new subjects are enrolled, until the assessment is complete. Based on its review, the DMC may make any of the following recommendations:

- Continue cohort and sequential dosing of cohorts as planned with additional safety monitoring and/or safety reviews as indicated
- Continue current cohort, but higher dose cohorts will receive lower doses than planned
- Decrease cohort dose and decrease doses of subsequent cohorts
- Extend temporary treatment discontinuation until additional data are available and/or further review/consultation occurs
- Permanently discontinue treatment for all cohorts
- Dose additional subjects of the cohort at the same dose

Cohort doses may be changed, based on DMC review of safety and efficacy data, to any dose between 0.5 µg/kg and 30 µg/kg. Any subject who discontinues from study drug will be encouraged to complete assessments for the duration of the study.

9.1.2 Dose Modifications for Efficacy

Dose modifications for efficacy are discussed in Section 9.1 (subsection *Optional, Open-label Extension Phase of the Study*).

9.2 Discussion of Study Design, Including Choice of Control Group

The intent and design of this Phase 2 study is to assess BMN 111 as a therapeutic option for the treatment of children with ACH. Children 5-14 years old with ACH were chosen because subjects with ACH have an *FGFR-3* gain of function mutation and because preliminary efficacy evaluation, determined by change in annualized growth velocity, requires treatment of subjects prior to epiphyseal growth plate closure, which occurs in late adolescence. Growth velocity in children with ACH remains relatively stable from approximately 3 years

old to growth plate closure (Hoover-Fong, 2008, Am.J Clin Nutr.). Children younger than 5 years old will not be enrolled in order to establish a safety profile in an older population first, as well as to minimize the confounding effects of nonlinear growth rates and inaccuracies inherent in measurement of recumbent length in young children. As children with ACH do not experience the normal physiological growth acceleration associated with puberty (Hoover-Fong, 2008, Am.J Clin Nutr.) that could confound the data, the population is not limited to pre-pubescent children. A maximum of five children from one gender may be enrolled in each cohort if the total size of the cohort is eight or nine subjects; a maximum of six children from one gender can be enrolled in each cohort if the size of the cohort is 10 subjects.

9.3 Selection of Study Population

Subjects 5-14 years old (inclusive) 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 9.3.1 and 9.3.2.

9.3.1 Inclusion Criteria

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

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 18 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.
2. Are 5 to 14 years old, inclusive, 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 assessment in Study 111-901 immediately before study entry, and have one documented standing height at least 6 months (+/- 10 days) prior to the screening visit for 111-202
5. Females $\geq$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 a highly effective method of contraception while participating in the study
7. Are ambulatory and able to stand without assistance
8. Are willing and able to perform all study procedures as physically possible

9. Parents or caregivers are willing to administer daily injections to the subjects

Additional Inclusion Criteria Optional, Open-label Extension Phase:

1. Appropriate written informed consent (and assent, if applicable)

9.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria are not 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:
   a. Hypothyroidism or hyperthyroidism
   b. Insulin-requiring diabetes mellitus
   c. Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others)
   d. Inflammatory bowel disease
   e. Autonomic neuropathy
   f. Recent acute illness associated with volume depletion (e.g., nausea, vomiting, diarrhea) that has not completely resolved prior to the first dose of the study drug
3. Have an unstable condition likely to require surgical intervention during the study (including progressive cervical medullary compression)
4. Growth plates have fused
5. Have a history of any of the following:
   a. Renal insufficiency, defined as creatinine > 2 mg/dl
   b. Anemia
   c. Baseline systolic BP < 75 mm Hg or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms i.e., dizziness, fainting) or recurrent symptomatic orthostatic hypotension
   d. Cardiac or vascular disease, including the following:
      i. Cardiac dysfunction (abnormal ECHO including abnormal LV mass) at Screening Visit
      ii. Hypertrophic cardiomyopathy
      iii. Pulmonary hypertension
      iv. Congenital heart disease with ongoing cardiac dysfunction

v. Cerebrovascular disease

vi. Aortic insufficiency

vii. Clinically significant atrial or ventricular arrhythmias

6. Have the following confirmed ECG findings:
   a. Right or left atrial enlargement or ventricular hypertrophy
   b. PR interval > 200 msec
   c. QRS interval > 110 msec
   d. Corrected QTc-F > 450 msec
   e. Second- or third-degree atrioventricular block
7. Documented Vitamin D deficiency (i.e., concentration of 25-hydroxy-vitamin D in the blood serum occurs at 12 ng/mL or less)
8. Require any investigational agent prior to completion of study period
9. Have received another investigational product or investigational medical device within 30 days 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
11. Current chronic therapy with antihypertensive medications, ACE inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function
12. Have been treated with growth hormone, IGF-1, or anabolic steroids in the previous 6 months or long-term treatment (> 3 months) at any time
13. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable)
14. Concomitant medication that prolongs the QT/QTc-F interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
15. Pregnant or breastfeeding at the Screening Visit or planning to become pregnant (self or partner) at any time during the study.
16. Have had limb-lengthening or bone-related surgery or expected to have limb-lengthening or bone-related surgery during the study period. Subjects with previous limb-lengthening or bone-related surgery may enroll if surgery occurred at least 18 months prior to the study and healing is complete without sequelae.
17. Have had a fracture of the long bones or spine within 6 months prior to screening (except for fracture of digits or toes)

18. Have AST or ALT at least 3x ULN or total bilirubin at least 2x ULN (except for subjects with known history of Gilbert's disease)
19. Evidence of severe sleep apnea requiring surgery or new initiation of CPAP (based on the screening sleep study)
20. Have current malignancy, history of malignancy, or currently under work-up for suspected malignancy
21. Have known hypersensitivity to BMN 111 or its excipients
22. Has 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
23. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, or would predispose the subject to hypotension (such as recent gastroenteritis or dehydration for any reason)
24. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the PI
25. Have a history of hip surgery or severe hip dysplasia
26. Have a history of clinically significant hip injury in the 30 days prior to screening
27. History of slipped capital femoral epiphysis or avascular necrosis of the femoral head
28. Are unable to lie flat when in prone position (needed for hip monitoring exam)

Additional Exclusion Criteria for Optional, Open-label Extension Phase:

1. Use of restricted therapies during the initial 6 months of the study
2. Permanently discontinued BMN 111 during the initial 6 months of the study

9.3.3 Removal of Subjects from Treatment or Assessment

Subjects (or their legally authorized representative) have the right to 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.

Investigators or subjects may suspend or discontinue administration of the investigational product. 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. For subjects who discontinue study drug but remain in the study, PK assessments will be waived completely; vital signs and clinical labs/biomarkers will be obtained only once at each visit subsequent to drug 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.

The Investigator (or designee) must contact the BioMarin Medical Monitor before a subject is discontinued by the Principal Investigator (PI) from either the study or from further study treatment. BioMarin reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual Investigator or study site for poor enrollment or noncompliance with the protocol or regulatory requirements.

Reasons for which a subject may be withdrawn from the study or from study treatment by either the Investigator or BioMarin include but are not limited to the following:

- Growth plates have closed
- Subject experiences a serious or intolerable AE
- Subject develops a clinically significant laboratory abnormality
- Subject requires medication or medical procedure prohibited by the protocol
- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up
- Subject becomes pregnant (refer to Section 10.3.1.9 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 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 or EC; hereafter collectively referred to as the ethics committee (EC). 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 (HIPAA) in the United States of America (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.

9.3.4 Subject Identification and Replacement of Subjects

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

Subjects who discontinued the study prior to Day 10 may be replaced upon discussion with the DMC. Subjects who discontinued the study after Day 10 of the initial phase will not be replaced.

Duration of Subject Participation

The planned subject participation in this study is 7 months for those subjects who do not continue in the optional, open-label extension phase, and 25 months for subjects who continue. Subjects will receive study treatment daily for 6 months in the initial phase, and 18 months in the optional, open-label extension phase for a total of up to 24 months. Following completion of 6 months, subjects who decline to participate in the extension phase will be followed for safety for an additional 1 month. The safety follow-up assessment will be a telephone call made weekly to the subject's legal guardian to assess for any AEs that may have occurred following completion of dosing. These subjects will return at Day 208 for the Safety Follow-Up visit and exit the study. For subjects who participate in the optional, open-label extension phase, following completion of Month 24, subjects will be followed for safety for an additional month to Month 25. Subjects who participate in the open-label extension phase of study 111-202 will have the option to enroll in the long-term extension study 111-205 at the Month 24/Study Completion Visit. The Month 25 Safety Follow up visit will be waived if a subject enrolls in the 111-205 extension study at the Month 24/Study Completion Visit.

Follow-up assessments and procedures should be performed as outlined in the 111-202 Schedule of Events (Table 9.1.1).

Subjects who discontinue from study treatment prior to Month 6 will be asked to complete study assessments and procedures for the remainder of the initial phase of the study. Subjects who discontinue from study treatment prior to Month 24 will be asked to complete study assessments and procedures for the remainder of the optional, open-label phase 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.

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, or the study is terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be administered BMN 111 during the study. The normal dosing schedule is 7 days a week.

9.4.1.1 BMN 111

During the study, subject assigned to receive BMN 111 will be administered one of the following daily dosing regimens:

- Cohort 1: daily morning dose of 2.5 µg/kg BMN 111
- Cohort 2: daily morning dose up to 7.5 µg/kg BMN 111
- Cohort 3: daily morning dose up to 15.0 µg/kg BMN 111
- Cohort 4: daily morning dose 30.0 µg/kg BMN 111

The injection sites should be alternated between doses. Doses may be administered in any of the common SC areas (upper arm, thigh, abdomen, buttocks [refer to Injection Guide for details]). Following administration of each dose, subjects will be observed for a minimum of 30 minutes (longer if clinically indicated) either in the clinic or at the subject's home (by home health nurse or parent or guardian). Instructions for home administration of study drug for subjects who qualify for parent or guardian administration are provided in the BMN 111 Injection Guide and Injection DVD.

9.4.2 Identity of Investigational Product

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 (CNP53). BMN 111 is a recombinant 39 amino acid peptide that includes the 37 C-terminal amino acids of the human CNP53 sequence, and modified by the addition of the 2 amino acids (Pro-Gly) on the N-terminus. 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 0.8 mg, 2 mg, or 10 mg lyophilized, preservative-free, white to yellow powder for reconstitution with sterile water for injection (WFI). The reconstituted solution is colorless to yellow and contains 0.2 mg/mL to 10 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. All reconstitution and dose preparation steps will be performed as indicated in the BMN 111 Injection Guide and Injection DVD.

The BMN 111 kit label includes the following information: the lot number, the required storage conditions, a precautionary statement, the expiry date, the study number, and BioMarin Pharmaceutical name and location.

9.4.3 Storage

At the study site, all study treatment 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 study treatment must be stored and inventoried and the inventories must be carefully and accurately documented according to applicable state, federal and local regulations, ICH GCP, and study procedures.

Specific information for storage and return of study drug is provided in the Pharmacy Manual.

9.4.4 Directions for Administration

Refer to the Injection Guide for complete study treatment preparation instructions. The date, time, volume, and concentration of each dose of study treatment administered to each subject must be recorded on the appropriate CRF, and (minus concentration) in the subject's study

workbook (if injection provided by parent/guardian) or nursing visit report (if injection is provided by Home Health Care Nurse [HHRN]).

BMN 111 will be administered in the morning as a single SC injection at the following doses: 2.5 µg/kg, up to 7.5 µg/kg, up to 15.0 µg/kg, and 30.0 µg/kg. Children should have an adequate breakfast. In the hour prior to injection, all subjects should have attempted to drink 8 ounces (~250 ml) of fluid (e.g. water, milk, juice, etc.), and the outcome must be documented by the site on clinic visit days.

Caregivers may administer study drug at home if approved by the Investigator and if adequate training is demonstrated. A parent/guardian may be eligible to administer study drug if he or she meets all of the following criteria:

- The subject has been on a stable dosing regimen for a minimum of 4 days
- PI has approved administration of study drug by the parent or guardian
- The parent or guardian 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 parent/guardian approval, a home health nurse may administer study drug or subjects may be administered drug in the clinic by study staff.

If a subject has experienced a CTCAE Grade 3 or higher AE that is considered possibly or probably drug-related, and/or a hypersensitivity reaction during the study, the subject's suitability for at-home drug administration will be evaluated by the Investigator and the Sponsor's Medical Monitor.

In the initial phase, on weeks when caregivers/subjects will not see either a home healthcare professional or a study staff member, a phone call by the study staff member to the caregiver/subject will be required. During the call study staff will ask the caregiver about correct administration procedures, assess adverse events (AEs), record concomitant medications, and answer questions. During the optional, open-label extension phase, the call frequency will change to every two weeks for the first 6 months of the extension phase and monthly thereafter.

Subjects who are eligible for at-home drug administration will be provided with Home-Administration Training Materials to supplement the in-person training provided by the qualified study site personnel. The Home-Administration Training Materials will include step-by-step instruction on the following:

- How to identify if the study drug is unsuitable for injection and how to report to the study site
- How to determine when to perform the injections and what is required immediately before performing the injections
- How to safely prepare and perform the injections of study drug
- How to make sure the subject is adequately hydrated
- How to receive, transport, track, store, prepare, and return both used and unused study drug kits
- How to safely use and dispose of syringes used for injections of study drug
- How to use a new syringe and vial every time drug is administered
- How to care for subject's injection site after an injection of study drug
- How to identify an adverse reaction and how to report this reaction to the study site and document it in the study provided subject workbook
- Who to contact at the study site in case of an emergency or concern/question
- How to determine in which instances to contact the local emergency telephone line

The Investigator or the Sponsor's Medical Monitor may request that drug administration by the parent be halted at any time and that the injections be performed by the study site personnel or home healthcare nurse.

9.4.5 Method of Assigning Subjects to Treatment Groups

No randomization schedule will be generated. All eligible subjects will receive BMN 111.

9.4.6 Selection of Doses Used in the Study

The protocol will utilize daily, subcutaneously administered, weight based, fixed-within-cohort dosing.

[redacted]

To date, clinical data in Study 111-202 demonstrated that BMN 111 was generally well tolerated at doses up to 30 µg/kg without evidence of abnormal growth.

9.4.7 Blinding

Study 111-202 is an open-label study. No blinding will be performed.

9.4.8 Selection of Timing of Dose for Each Subject

9.4.8.1 Prior and Concomitant Medications

All medications (prescription, over-the-counter [OTC] and herbal), and nutritional supplements 30 days prior to screening and throughout the study will be recorded on the designated CRF. 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 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 CRF. Concomitant medication information will be collected at the time points indicated in the Schedule of Events (Table 9.1.1).

The following medications are excluded during the screening period through completion of the study:

- Growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids
- ACE inhibitors, cardiac glycosides, calcium channel blockers, beta blockers, or antihypertensive medications

- Diuretics
- Probenecid, or other drugs known to alter renal or tubular function
- Concomitant medication that prolongs the QT/QTc-F interval
- Any other investigational product for the treatment of ACH or short stature

9.4.9 Treatment Compliance

The date, time, volume, and concentration of each dose of study drug administered to each subject must be recorded. These data will be used to assess treatment compliance.

9.5 Investigational Product Accountability

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 dose specific accounting), and IP lost or accidentally or deliberately destroyed, or there was a temperature excursion and the IP is not usable. The Investigator or designee must retain all used, unused, or expired IP until the study monitor (on-site CRA) has confirmed the accountability data. Returned ancillary supplies will be destroyed per site SOP. Investigational Product accountability should be completed per the Schedule of Events, Table 9.1.1.

9.5.1 Return and Disposition of Clinical Supplies

Used and unused study investigational product must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide written explanation for any destroyed or missing study investigational product or study materials.

Used and unused study investigational product may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The study monitor must account for all study investigational product in a formal reconciliation process prior to study investigational product destruction. Unused IP may only be destroyed if the study site can also provide a certificate of destruction or a receipt for destruction whenever unused IP is destroyed. All study investigational product destroyed on site must be documented. Documentation must be provided to BioMarin and retained in the Investigator study files. If a site is unable to destroy study investigational product appropriately, the site must return unused and used study investigational product to BioMarin drug distribution center upon request. The return of study treatment or study treatment materials must be accounted for on a Study Drug Return Form located in the Pharmacy Manual. All study investigational product and related materials should be stored,

inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

Parents or guardians of subjects who qualify for home administration of study investigational product will be provided with instructions for returning used and unused study investigational product and the proper disposal of any study drug materials (refer to the Home Administration Training/Patient Materials section in the Study Reference Manual).

9.6 Dietary or Other Protocol Restrictions

BMN 111 will be administered in the morning as a single SC injection. Children should have an adequate breakfast. In the hour prior to injection, all subjects should have attempted to drink 8 ounces (~250 ml) of fluid (e.g. water, milk, juice, etc.), and the outcome must be documented by the site on clinic visit days.

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 Parent Standing Height

The standing height of the participant's biological parents will be assessed if they agree to participate. Prior to the measurement, each parent is required to complete an ICF specific to this optional parent height assessment.

9.9 Physical Examination Findings

Physical examination will include assessment of general appearance; CV; dermatologic; head, eyes, ears, nose, and throat; lymphatic; respiratory; GI; musculoskeletal; and neurological/psychological and genitourinary. Tanner stage of Pubertal Development will also be assessed. The reference to the Tanner stage assessment document is included in the Study Reference Manual. Other body systems may be examined. Day 1 results will be the baseline values and clinically significant changes from baseline will be recorded as an AE or SAE as appropriate.

9.10 Efficacy and Safety Variables

9.10.1 Efficacy and Safety Measurements Assessed

The Schedule of Events in Section 9.1 describes the timing of required evaluations.

9.10.2 Efficacy Variables

Efficacy will be assessed by change from baseline in height growth velocity (annualized to cm/year), growth parameters, and in body proportions. These changes 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 and leg, hand and foot. Upper arm to forearm length ratio, upper leg to lower leg length ratio, and upper to lower body segment ratio will be calculated.

The following growth measures may be collected approximately the same time each day (±2 hours around the time of first measurement assessment, including Screening measurement assessment) by a study staff member, preferably the same person throughout the study, who has been trained by a BioMarin representative. Measurements not taken in the midsagittal plane should be taken on the right side of the body when possible. Measurements may include but are not limited to standing height, sitting height, head circumference, upper and lower arm and leg, hand and foot. Standardized measuring equipment and detailed measurement techniques are detailed in the Anthropometric Guidelines.

The following ratios will be calculated:

- Upper arm to forearm length ratio
- Upper leg to lower leg length ratio
- Upper to lower body segment ratio

Additional ratios may be calculated.

Weight will be measured at Screening and at each in-clinic dosing visit.

9.10.2.1 Pharmacokinetic Variables

In the initial phase of the study, on Days 1, 10, 29, 85, and 183, PK plasma samples are collected pre-dose and at 5 (±2 min), 15 (±2 min), 30 (±5 min), 60 (±5 min), 90 (±5 min), 120 (±5 min) min, and 180 (±5 min) min post-dose as indicated in Table 9.1.1 and are considered to represent full PK sampling.

Whenever possible, the following PK parameters will be estimated by non-compartmental analysis for Days 1, 10, 29, 85, and 183:

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

- C_{max}
- T_{max}
- Elimination half-life ($t_{1/2}$)
- Apparent clearance of drug (CL/F)
- Apparent volume of distribution based upon the terminal phase (V_z/F)

Dose proportionality and drug accumulation after repeat dose administration will also be evaluated. PK parameters at Day 183 will be compared to Days 1, 10, 29, and 85 to determine if time related changes in exposure and clearance occur.

For subjects whose dose does not change in the optional, open-label extension phase, full PK samples will be taken at Months 12 and 24. Partial PK samples will be taken at four time points (pre-dose, 15, 30, and 60 minutes post dose) to estimate exposure and to correspond with immunogenicity assessments. These partial PK draws will take place at Months 8, 10, 15, 18, and 21 with immunogenicity assessments.

For subjects whose doses are adjusted in the optional, open-label extension phase, full PK samples will be drawn at the dose adjustment visit, even if the dose adjustment visit falls on a regularly scheduled visit where a partial PK is otherwise indicated. At subsequent visits, full or partial PK will be drawn per collection schedule in Table 9.10.2.1.1. Note: PK sample schedule does not change following dose adjustment.

Table 9.10.2.1.1: PK Sample Schedule

Initial Phase						
Day						
1	10	29	85	183		
Full[a]	Full	Full	Full	Full		
Optional, Open-label Extension Phase						
Month						
8	10	12	15	18	21	24
Partial[b]	Partial	Full	Partial	Partial	Partial	Full

[a] **Full PK** plasma samples are collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 60 (± 5 min), 90 (± 5 min), 120 (± 5 min), and 180 (± 5 min) minutes post-dose.

[b] **Partial PK** samples are collected at four time points: pre-dose, 15 (± 2 min), 30 (± 5 min), and 60 (± 5 min) minutes post-dose.

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

9.10.3 Exploratory Efficacy Variables

Flexion-extension measures of elbow joint range of motion will be measured with a goniometer. Refer to the instructional guidelines for elbow joint range of motion, located in Study Reference Manual.

9.10.3.1 Pharmacodynamic Variables

Biomarkers will be evaluated by change from baseline and may include but are not limited to assessment for cartilage turnover (CTX-II), chondrocyte and osteoblast activity (bone-specific alkaline phosphatase), bone formation (P1NP), bone turnover (osteocalcin); and markers of BMN 111 bioactivity (cGMP, NT-proCNP, and ANP) as well as additional exploratory biomarkers. BioMarin or designee will perform analysis, and samples may also be used for assay development.

Samples for blood and urine biochemical markers of collagen and bone turnover, and for markers of BMN 111 activity, will be collected at the time points presented in Table 9.1.1. Refer to the Laboratory Manual for instructions regarding obtaining and shipping samples. The testing facility and sample type will also be included in the Laboratory Manual.

9.10.3.1.1 Biomarker Research Sample Analyses

All biomarker samples collected in this study may be used for exploratory biomarker research including evaluation of additional biomarkers not specifically listed in Section 9.10.3.1. In addition, samples collected for other purposes may be used for exploratory use once the primary use has been completed.

9.10.3.2 Sleep Apnea

Untreated sleep apnea in childhood has been repeatedly associated with poor functional and health outcomes, including negative impacts on certain aspects of child development such as behavior and learning. Cognitive deficits reported to be associated with sleep apnea in children include learning, memory, and visual-spatial skills; language, verbal fluency, school performance and executive functions. In addition, pediatric sleep-disordered breathing has been associated with growth abnormalities; alterations in cardiac health, including both systolic and diastolic blood pressure, autonomic regulation, brain oxygenation, and cerebral blood flow, suggesting that childhood obstructive sleep apnea syndrome may jeopardize long-term cardiovascular health; and systemic markers of inflammation

(Marcus, 2012, Pediatrics). Given that sleep apnea is a finding in children with ACH (Waters, 1993, Arch.Dis.Child), and its implications on functional and health outcomes, a sleep-testing device (sleep testing is conducted at a certified sleep center) will be used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring at Screening and on Days 85 and 183 of the initial phase, and Months 12 and 24 of the optional, open-label extension phase, and at Early Termination if subject discontinues after 18 months. 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, AHI). If sleep apnea reading is not accurate, subject may need to repeat assessment the next day.

9.10.3.3 Imaging Assessment Procedures (per Schedule of Events)

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

- AP x-ray of pelvis for baseline hip assessment.
- Posterior-anterior (PA) radiographs of the left hand and wrist to assess bone age (Greulich, 1971, Stanford University Press.); (Tanner, 1975, Academic Press.), growth plates, hand length, and cortical thickness.
- Anterior-posterior (AP) lower extremity radiograph to assess growth plates, tibial length, cortical thickness, and bowing.
- AP radiographs of lumbar spine to assess transverse interpedicular distance. An AP x-ray of spine will also be assessed at screening for the purpose of landmarking.
- Lateral radiographs of lumbar spine to assess, thoracolumbar lordosis angle, vertebral morphology, as well as other potential changes related to spinal stenosis.
- QCT scan of forearm and tibia to assess bone mineral density, growth plate morphology, and bone length. This scan will be acquired with a standard CT scanner, calibration phantom, and designated software, using a predetermined low radiation dose protocol, which avoids direct radiation to the head and torso.

Should subjects' imaging assessment yield any concerns, additional imaging may be conducted; this will be determined by the Principal Investigator in conjunction with the BioMarin Medical Monitor and the DMC if indicated. Imaging assessments will be collected and interpreted by a central reader, except for AP X-ray of the pelvis, which will be reviewed by a local radiologist and the PI to determine clinical significance. Refer to the Imaging Guidelines (Bioclinica and eRT) for detailed imaging assessment requirements and procedures.

9.10.4 Safety Variables

Safety will be evaluated by the incidence of AEs, SAEs, and clinically significant changes in vital signs, physical examination, ECG and ECHO results, imaging, anti-BMN 111 immunogenicity assessments, and laboratory test results (urinalysis, chemistry, hematology). Additionally, imaging, hip monitoring, biomarker, and physical measurement data, including elbow joint range of motion measured with goniometer, will be utilized for safety-related reviews and analysis.

9.10.4.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. 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 Table 9.1.1. Additionally, site staff will contact study subjects by telephone at minimum once a week during the initial phase of the study to assess AEs, and once every 2-4 weeks during the optional, open-label extension phase.

9.10.4.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1. The scheduled clinical laboratory tests are listed in Table 9.1.1. Refer to the Laboratory Manual for instructions on obtaining and shipping samples.

Any abnormal test results determined to be clinically significant by the Investigator 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.

All clinical laboratory result pages and AP pelvis X-ray reports should be initialed and dated by an Investigator or acceptable designee, along with a comment regarding whether or not an abnormal result is clinically significant. Each clinically significant laboratory result should be recorded as an AE in the CRF.

The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the AE CRF (Section 10.3.1.4).

Table 9.10.4.2.1: Clinical Laboratory Tests

Blood Chemistry	Hematology	Urinalysis
Albumin	Hemoglobin	Appearance
Alkaline phosphatase, total	Hematocrit	Color
ALT (SGPT)	WBC count	pH
AST (SGOT)	RBC count	Specific gravity
Direct bilirubin	Platelet count	Ketones
Total bilirubin	Differential cell count	Protein
BUN		Glucose
Calcium		Bilirubin
Chloride		Nitrite
Potassium		Urobilinogen
Sodium		Hemoglobin
Total cholesterol		
Uric acid		
Glucose		
GGT		**Biomarkers**
LDH		BMN 111 activity biomarkers
Phosphorus		Bone and collagen biomarkers
Total protein		Urine Chemistry
Vitamin D		Sodium
Creatinine		Potassium
Alkaline phosphatase, bone-specific		Creatinine
Thyroid function (TSH, T3, free T4)		
Blood Special Chemistry		
BMN 111 activity biomarkers		
Bone and collagen biomarkers		
Anti-BMN 111 antibodies		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cell.

9.10.4.3 Other Laboratory Assessments

Subjects will be asked to provide serum and urine at the times indicated in the Schedule of Events (Table 9.1.1).

For subjects who have not 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 certification with the study specific mutation documented.

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

9.10.4.4.1 Vital Signs

Vital signs 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 assessments include heart rate and BP. On visit Days 1, 2, 3, and 4, minimum assessment frequency is every 15 min (±5 min) for 2 hours post dose; and assessment is taken every 30 min (±5 min) from 2 to 4 hours post dose. On visit Days 1 and 2, 4 to 8 hours post-dose measurements are taken every 60 min (±10 min). For all other dosing visits, assessment is every 15 min (±5 min) for the first hour post dose and a final assessment prior to the end of the visit (if longer than 1 hour). Vital sign assessment frequency is presented in Table 9.10.4.4.1.1.

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 timepoint in a sitting position after at least 5 minutes of rest. Heart rate should be taken at each timepoint 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. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated (Table 9.1.1).

Table 9.10.4.4.1.1: Vital Sign Assessment Frequency

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.			
	Assessment Frequency			
Dosing Visits	0-1 hr post-dose	0-2 hr post-dose	2-4 hr post dose	4-8 hr post-dose
Days 1, 2		q 15 min (± 5 min)	q 30 min (± 5 min)	q 60 min (± 10 min)
Days 3, 4 and dose adjustment visit in optional, open-label extension phase		q 15 min (± 5 min)	q 30 min (± 5 min)	
All other dosing visits	q 15 min (± 5 min); final assessment prior to end of visit (if longer than 1 hr). Includes dose adjustment and follow up visits.			

1. Vital sign measurements are taken once per timepoint in a sitting position after at least 5 minutes of rest.
2. Left brachial arm should be the first method of assessment considered, and the same site should be used for measurement of BP in each subject throughout the study.
3. Heart rate should be taken at each timepoint that BP is measured.
4. 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.
5. 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.
6. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
7. If a subject has a hypotensive event (or 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.

9.10.4.4.2 Mitigating the Risk of Potential Hypotension

Study personnel and caregivers should be aware of the potential risk of hypotension with BMN 111 administration. Subjects must be well hydrated and have eaten breakfast prior to administration of BMN 111. In the hour prior to injection, all subjects should have attempted to drink 8 ounces (~250 ml) of fluid (e.g. water, milk, juice, etc.), and the outcome must be documented by the site on clinic visit days. Caregivers should be trained to observe and recognize the symptoms of dehydration (e.g. from fever, vomiting, diarrhea, etc.) and contact the Investigator prior to study drug 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.

9.10.4.4.3 Hip Monitoring

Baseline hip assessments will be conducted for all cohorts, and will include medical history, physical exam, and AP x-ray of the pelvis. Subsequent hip monitoring assessments will be conducted at regular 6-month intervals. Medical history will be obtained to evaluate for hip, thigh, or knee pain, or change in gait. The physical exam will include supine and prone assessment to determine pain or limitation with hip range of motion and internal/external rotation of hip joint. Changes from baseline will trigger further evaluation, which may include additional hip imaging, and/or orthopedic consultation. DMC will be notified of abnormal results from hip monitoring assessments to determine if/when BMN 111 treatment should be temporarily or permanently discontinued, or dose reduced.

9.10.4.4.4 ECGs

A standard 12-lead ECG will include heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. If clinically significant abnormalities are noted, the Investigator or designee is required to assess whether it is appropriate for the subject to continue in the study. ECGs will be performed at the time points indicated in the Schedule of Events (Table 9.1.1).

9.10.4.4.5 ECHO

Cardiac anatomy and function will be evaluated by a standard 2-dimensional Doppler ECHO. The data recorded is to include ventricular cavity size, valve characterization (presence or absence of valve stenosis or regurgitation and clinical significance), ventricular wall thickness, regional wall motion, LV mass calculation, and pericardial characterization. ECHOs will be performed at the time points indicated in the Schedule of Events (Table 9.1.1).

9.10.4.4.6 Anti-BMN 111 Immunogenicity Assessments and IgE Testing

9.10.4.4.6.1 Scheduled Immunogenicity Assessments

Blood serum sampling for immunogenicity assessments will be performed at the time points indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2).

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

- Anti-BMN 111 total antibody (TAb)
- Endogenous CNP, ANP, and BNP cross-reactivity
- Anti-BMN 111 neutralizing antibody (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-BMN111 TAb-positive samples.

9.10.4.4.6.2 Ad Hoc Safety Assessments

Samples for total IgE and drug-specific IgE testing will be drawn pre-dose on Day 1. If a significant hypersensitivity adverse event (defined as grade 3 or higher, or requiring temporary or permanent cessation of BMN 111, or at the discretion of Investigator and/or BioMarin, excluding reactions that are solely a localized injection site reaction) occurs, an unscheduled safety visit should occur within 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:

- Anti-BMN 111 IgE (drug-specific IgE)
- Total IgE
- Serum tryptase

If feasible, a sample for drug-specific IgE should be drawn at least 8 hours after the event start time and before the next dose. A sample for total IgE and serum tryptase should also be drawn within an 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, i.e., 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).

9.10.4.5 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). Female subjects with a positive pregnancy test at Screening do not meet eligibility criteria for enrollment (Section 9.3.2).

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

Refer to Section 10.3.1.9 for details on the reporting procedures to follow in the event of pregnancy.

9.11 Pediatric Blood Volume

Clinical labs and immunogenicity samples are relevant to safety assessment in this study. The objective of the PK assessments is to understand the relationship between exposure and biologic activity. The objectives of exploring pharmacodynamic activity biomarkers are to demonstrate biologic activity of BMN 111 and to understand both the impact of immune responses on drug activity and the mechanisms of CV changes during dosing; and for bone and collagen biomarkers, to demonstrate activity at the growth plate (chondrocyte) and bone (osteoblast) levels.

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.

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 (e.g., 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.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

10.1.2 Serious Adverse Events

A serious adverse event (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 patient 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. Hospitalization for less than 24 hours will not be considered to be an SAE.

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child or fetus of a patient exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction that, based on medical judgment, may jeopardize the patient or require intervention to prevent one of the above consequences (e.g., anaphylaxis)

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

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. The Month 25 Safety Follow-up Visit will be waived if a subject enrolls in the 111-205 extension study at the Month 24/Study Completion Visit. The criteria for determining, and the reporting of SAEs are provided in Section 10.1.2.

10.2.2 Eliciting Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs should be recorded in the patient's medical record and on the AE Case Report Form (CRF).

10.2.3 Assessment of Seriousness, Severity, and Causality

The Investigator responsible for the care of the patient or medically qualified designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.1.2 for SAE definitions). These assessments should 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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient'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 using the 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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be reported as SAEs
5	Death related to an AE	

[a] Instrumental ADL refer 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 patient 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 MedDRA (Medical Dictionary for Regulatory Activities) 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 or symptom. 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 patient 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 patient evaluation time points, but then subsequently recurs. All recurrences of the AE are considered separate events and should be recorded as such on the AE eCRF.

10.3.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

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 any one or more of the following conditions is met:

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

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.

10.3.1.5 Pre-existing Conditions

A pre-existing condition is one that is present at the start of the study. 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 (e.g., worsening back pain).

10.3.1.6 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition (refer to Section 10.3.1.5). 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.

10.3.1.7 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 efficacy measurement
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Receive scheduled therapy (study drug or otherwise) for the study indication

10.3.1.8 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.

10.3.1.9 Pregnancy

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

Pregnancy in a patient or partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing the Pregnancy Form in the study reference materials to BPV. The pregnancy reporting period begins following first dose of study drug and 4 weeks after last dose of study drug. In addition, pregnancy in a patient is also reported on the End of

Study eCRF. The Investigator must make every effort to follow the patient through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials. In the event of pregnancy in the partner of a study patient, 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

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 BioMarin Pharmacovigilance (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 Reporting Requirements

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

10.5 Follow-up of Patients after Adverse Events

The Investigator should follow all unresolved AEs/SAEs until the events are resolved or have stabilized, the patient 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 patient'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 (e.g., hospital discharge summary, consultant report, or 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 patient to report, to the Investigator and/or to BPV directly, any subsequent SAEs that the patient'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 patient 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 patient 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 patients against any immediate hazards that may affect the safety of patients, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) 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 patients, the sponsor and the Investigator shall take appropriate urgent safety measures to protect the patients 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/EC/REB is notified at the same time."

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 (ETV). 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 or 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: [redacted], MD, PhD
Address: BioMarin
Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949 USA
Phone: [redacted]
Fax:
E-mail:

11 STUDY PRODCEDURES

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

Written informed consent and assent, as appropriate, after the nature of the study has been explained must be obtained prior to any research-related procedures. 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)
- Medical history, including growth history and ACH-related history
- Genetic testing (if needed)
- Physical examination
- Tanner Stage of Pubertal Development
- Weight
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Anthropometric measurements
- Elbow joint range of motion
- Baseline hip assessment, including AP x-ray of pelvis
- Sleep apnea assessments
- ECG
- ECHO
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Thyroid function tests
- Serum glucose levels
- Vitamin D
- Pregnancy test (urine or serum) for female subjects who have begun menses or are $\geq$10 years old
- PD BMN 111 activity biomarkers (NTproCNP only [plasma])
- PD Bone and collagen biomarkers (all)
- QCT of forearm and tibia
- Bone age x-ray (PA of hand and wrist)

- AP lower extremity radiograph
- Lateral lumbar spine x-ray
- AP x-ray of spine
- Concomitant medications
- Adverse events

11.2 Treatment Visits

11.2.1 Day 1 (no visit window)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- PD BMN 111 activity biomarkers (all except NTproCNP)
- PD Bone and collagen biomarkers (all except osteocalcin)
- Anti-BMN 111 immunogenicity assessments
- PK (full)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.2 Days 2 and 3, (no visit window)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.3 Day 4 (no visit window)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- Clinical labs (hematology, chemistry, and urinalysis)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.4 Day 10 (±1 Day)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- PD BMN 111 activity biomarkers (cGMP and ANP)
- PD Bone and collagen biomarker (BSAP only)
- Anti-BMN 111 immunogenicity assessments
- PK (full)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.5 Day 15 (±1 Day)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- Clinical labs (hematology, chemistry, and urinalysis)

- Urine chemistry
- PD BMN 111 activity biomarkers (cGMP only)
- PD Bone and collagen biomarkers (all except osteocalcin)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.6 Day 22 (±1 Day)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- Urine chemistry
- PD Bone and collagen biomarker (CTX-II urine only)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.7 Day 29 (±1 Day)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- PD BMN 111 activity biomarkers (all)
- PD Bone and collagen biomarkers (all except osteocalcin)
- Anti-BMN 111 immunogenicity assessment(s)
- PK (full)
- Concomitant medications

- Study drug administration
- Study drug accountability
- Adverse events

11.2.8 Day 43 (±7 Days)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Anthropometric measurements
- Weight
- Pregnancy test (urine or serum) for female subjects who have begun menses or are ≥10 years old
- Elbow joint range of motion
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- PD BMN 111 activity biomarker (cGMP and NTproCNP only)
- PD Bone and collagen biomarkers (all except osteocalcin)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.9 Day 85 (±7 Days)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Anthropometric measurements
- Weight
- Pregnancy test (urine or serum) for female subjects who have begun menses or are ≥10 years old
- Elbow joint range of motion
- Sleep apnea assessments
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)

- Urine chemistry
- PD BMN 111 activity biomarkers (cGMP only)
- PD Bone and collagen biomarkers (all except osteocalcin)
- Anti-BMN 111 immunogenicity assessment(s)
- PK (full)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.9.1 Day 127 (±7 Days)

- Physical examination
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Anthropometric measurements
- Weight
- Pregnancy test (urine or serum) for female subjects who have begun menses or are ≥10 years old
- Elbow joint range of motion
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- PD BMN 111 activity biomarkers (all)
- PD Bone and collagen biomarkers (all except osteocalcin)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.2.9.2 Day 183 Month 6 (±7 Days)

- Informed consent for optional, open-label extension phase
- Physical examination
- Tanner Stage of Pubertal Development

- 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
- Elbow joint range of motion
- Hip monitoring
- Sleep apnea assessments
- ECG
- ECHO
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Thyroid function tests
- Serum glucose levels
- Vitamin D
- PD BMN 111 activity biomarkers (all except ANP)
- PD Bone and collagen biomarkers (all)
- Anti-BMN 111 immunogenicity assessment(s)
- PK (full)
- QCT of forearm and tibia
- Bone age x-ray (PA of hand and wrist)
- AP lower extremity radiograph
- Lateral lumbar spine x-ray
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.3 Safety Follow-Up Visits

11.3.1 Day 208 (±7 Days)

- Physical examination
- 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)
- Elbow joint range of motion
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Anti-BMN 111 immunogenicity assessments
- Concomitant medications
- Adverse events

11.3.2 Early Termination (6-Month Initial Phase)

- Physical examination
- Tanner Stage of Pubertal Development
- 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 Day 43)
- Weight
- Elbow joint range of motion
- Hip monitoring
- Sleep apnea assessments
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Vitamin D
- PD BMN 111 activity biomarkers (NTproCNP only)

- PD Bone and collagen biomarkers (all)
- Anti-BMN 111 immunogenicity assessments
- Bone age x-ray (PA of hand and wrist) (obtained only if the subject discontinues after Day 60)
- AP lower extremity radiograph (obtained only if the subject discontinues after Day 60)
- Concomitant medications
- Study drug accountability
- Adverse events

11.4 Optional, Open-label Extension Visits

The optional, open-label extension phase of the study will run through Month 25. However, the Month 25 Safety visit will be waived if a subject enrolls in the 111-205 extension study at the Month 24/Study Completion Visit.

11.4.1 Month 8 (±7 days)

- Physical examination
- 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
- Elbow joint range of motion
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Anti-BMN 111 immunogenicity assessments
- PD bone and collagen biomarkers (all except osteocalcin)
- PK (partial)
- Concomitant medications
- Study drug administration
- Study drug accountability

- Adverse events

11.4.2 Months 10 (±7 days), 15 (±14 days), and 21 (±14 days)

- Physical examination
- 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
- Elbow joint range of motion
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Anti-BMN 111 immunogenicity assessment(s)
- PD bone and collagen biomarkers (all except osteocalcin)
- PK (partial)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.4.3 Month 12 (±7 days)

- Physical examination
- Tanner Stage of Pubertal Development
- 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
- Elbow joint range of motion
- Hip monitoring
- Sleep apnea assessments

- ECG
- ECHO
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Anti-BMN 111 immunogenicity assessment(s)
- PD BMN 111 activity biomarkers (all)
- PD bone and collagen biomarkers (all)
- PK (full)
- QCT of forearm and tibia
- Bone age x-ray (PA of hand and wrist)
- AP lower extremity radiograph
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.4.4 Month 18 (±14 days)

- Physical examination
- Tanner Stage of Pubertal Development
- 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
- Elbow joint range of motion
- Hip monitoring
- ECG
- ECHO
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry

- Anti-BMN 111 immunogenicity assessment(s)
- PD BMN 111 activity biomarkers (cGMP only)
- PD bone and collagen biomarkers (all except osteocalcin)
- PK (partial)
- Bone age x-ray (PA of hand and wrist)
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.4.5 Month 24/Study Completion Visit (±14 days)

- Physical examination
- Tanner Stage of Pubertal Development
- 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
- Elbow joint range of motion
- Hip monitoring
- Sleep apnea assessments
- ECG
- ECHO
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Thyroid function tests
- Vitamin D
- Anti-BMN 111 immunogenicity
- PD BMN 111 activity biomarkers (all)
- PD bone and collagen biomarkers (all)

- PK (full)
- QCT of forearm and tibia
- Bone age x-ray (PA of hand and wrist)
- AP lower extremity radiograph
- Lateral lumbar spine x-ray
- AP x-ray of spine
- Concomitant medications
- Study drug administration
- Study drug accountability
- Adverse events

11.5 Safety Follow-Up Visits

11.5.1 Month 25 (±7 days)

- Physical examination
- 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
- Elbow joint range of motion
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Anti-BMN 111 immunogenicity assessment(s)
- Concomitant medications
- Adverse events

11.5.2 Early Termination (Optional, Open-Label Extension Phase)

- Physical examination
- Tanner Stage of Pubertal Development
- 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
- Elbow joint range of motion
- Hip monitoring
- Sleep apnea assessments (only if subject discontinues after 18 months)
- ECG
- ECHO
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- Vitamin D
- Anti-BMN 111 immunogenicity assessment(s)
- PD BMN 111 activity biomarkers (NTproCNP only)
- PD bone and collagen biomarkers (all)
- QCT of forearm and tibia (only if the previous assessment was done more than 60 days prior to early termination)
- Bone age x-ray (PA of hand and wrist) (only if the previous assessment was done more than 60 days prior to early termination)
- AP lower extremity radiograph (only if the previous assessment was done more than 60 days prior to early termination)
- Lateral lumbar spine x-ray (only if the subject discontinues after 18 months)
- AP x-ray of spine (only if the subject discontinues after 18 months)
- Concomitant medications
- Study drug accountability
- Adverse events

11.6 Dose Adjustment Visits

See Table 9.10.2.1.1. Full PK is to be conducted on the Day 1 transition to next higher dose per Table 9.10.2.1.1.

11.6.1 If the Next Scheduled Visit is ≤4 Weeks Away, Dose Adjustment Takes Place at the Next Scheduled Visit

The procedures below are done at adjustment visits. If the adjustment visit happens at a regularly scheduled visit, conduct the remaining scheduled visit procedures as well.

- Physical exam
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- Anthropometry
- ECG
- Clinical labs
- Urine chemistry
- Full PK
- Concomitant meds
- Drug administration
- Drug accountability
- Adverse events

11.6.2 If the Next Scheduled Visit is >4 Weeks Away, Dose Adjustment Takes Place at an Unscheduled Visit Within 4 Weeks From DMC Decision To Dose Adjust

- Physical exam
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Anthropometry
- Weight
- ECG
- Clinical labs (hematology, chemistry, and urinalysis)
- Urine chemistry
- PK (full)
- Concomitant meds
- Drug administration
- Drug accountability

- Adverse events

11.7 7-10 Day Post-dose Adjustment

- Phone call

11.8 4 Weeks Post Dose Adjustment Follow-up Visit Assessments (±2 weeks)

If a regular or unscheduled visit occurs within the ± 2-week visit window, follow-up visit can be waived. The procedures below are done at adjustment follow-up visits. If the adjustment follow-up visit happens at a regularly scheduled visit, conduct the remaining scheduled visit procedures as well.

- Physical exam
- Vital signs (body temperature, heart rate, BP, respiratory rate)
- Weight
- Clinical labs
- ECG
- Concomitant meds
- Drug administration
- Drug accountability
- Adverse events

12 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, CRFs, 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.

Data quality control and analysis will be performed by BioMarin or a designee, based on a predefined analysis plan.

13 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

13.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS.

13.1.1 Interim Analyses

No formal interim analyses for efficacy are planned for this study. However, efficacy data from the first three cohorts may be evaluated to inform internal decision-making regarding Cohort 4. Efficacy data may also be used to inform the decision to increase a cohort dose if the initial dose exhibits suboptimal efficacy. To address objectives of the study, formal analyses will be performed when all subjects have completed the initial 6-month phase and when all available subjects have completed the extension phase. Additional exploratory analyses may be performed in the extension phase.

13.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

No imputation of missing data is planned for this study.

13.2 Efficacy Analysis

Efficacy analysis will be carried out for the initial 6-month period and the extension period. For each of the two periods, all subjects who receive at least one dose of study treatment and who have post-treatment data in the corresponding period for any efficacy endpoint will be included in the efficacy analysis for that endpoint. The baseline of the growth velocity is established in the natural history study of BMN 111-901, based on the standing height measurements in the last 6 months prior to enrollment to BMN 111-202. The baseline for other efficacy endpoints is defined as the last non-missing assessment prior to the first dose.

Annualized growth velocity, based on standing height measures at every 6-month time point, will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum). The test of hypothesis of no change from the baseline in annualized growth velocity will be conducted via paired t-test for the initial 6-month period and p-value will be considered descriptive. Change in body proportion ratios (upper arm to forearm length ratio, upper leg to lower leg length ratio, and upper to lower body segment ratio) from baseline to each scheduled time point will be similarly summarized and tested at the initial 6-month time point. The measurement of height will be converted to age-and sex-appropriate standard score (SDS), also referred to as Z-score, by comparison with normal reference standards (not ACH). The Z-score will be summarized similarly to growth velocity. Results will be summarized by dose cohort and for all cohorts combined.

Other anthropometric measures (sitting height, weight, head circumference, upper and lower arm and leg, hand and foot, etc.) will be summarized at each time point and will be evaluated for changes from baseline.

13.3 Pharmacokinetic Analyses

PK parameters will be summarized using descriptive statistics. Results will be summarized by dose cohort.

13.3.1 Exploratory Analyses

Exploratory analyses will be carried out for the initial 6-month period and the extension period, respectively.

13.3.1.1 Biomarker Analysis

Biomarkers include, but are not limited to, assessment for cartilage turnover (CTX-II), chondrocyte and osteoblast activity (BSAP), bone formation (P1NP), osteocalcin; and markers of BMN 111 bioactivity (cGMP, NT-proCNP, and ANP). These biomarker measures will be summarized by change from baseline by study time point. Results will be summarized by dose cohort. Additionally, the biomarkers may be assessed for the correlations with clinical outcomes.

13.3.1.2 Sleep Apnea Analysis

The numerical variables of sleep apnea analysis will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum) and the categorical variables will be summarized by number and percentage of subjects.

13.3.1.3 Imaging Assessment Analysis

Changes from baseline to end of study in measures of vertebral height imaging assessment of the lumbar spine, QCT of the forearm and tibia will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum) and will be tested via paired t-test. The p-value will be considered descriptive. Changes from baseline in bone density and bone quality will be similarly summarized and tested. Results will be summarized by dose cohort.

13.3.1.4 Immunogenicity Analysis

Immunogenicity will be summarized by change from baseline as well as by study timepoint. Results will be summarized by dose cohort and for all cohorts combined. Additionally, immunogenicity may be assessed for correlations with measures of safety, PK, and efficacy.

13.3.1.5 Elbow Joint Range of Motion

The value and change from baseline in the elbow joint range of motion to each scheduled time point will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum). Results will be summarized by dose cohort.

13.4 Safety Analysis

Safety analysis will be carried out for the initial 6 months period and the extension period, respectively. For each of the two periods, all subjects who receive at least one dose of study treatment in this study and have any post-treatment safety information in the corresponding period will be included in the safety analysis. The safety analysis will be descriptive and will be summarized by dose cohort and all cohorts combined.

All AEs will be coded using the current version of 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, 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 laboratory tests, vital signs, ECG, and concomitant medication data will also be summarized descriptively. Laboratory tests will also be summarized by absolute and percent change from baseline and listed for each dose cohort and for all cohorts combined. Vital signs, ECG and ECHO results will also be listed. The baseline for laboratory tests and ECG is defined as the last non-missing assessment prior to the first dose.

13.5 Determination of Sample Size

Approximately 36 pediatric subjects with ACH will participate in this study. No formal sample size calculations were performed.

13.6 Analysis Populations

The following populations will be defined for the initial 6-month period and the extension period, respectively.

Safety Analysis: For each of initial 6-month period and the extension period, all subjects who receive at least one dose of study treatment in this study and have any post treatment safety information in the corresponding period will be included in the safety analysis.

Efficacy Analysis: For each of initial 6-month period and the extension period, all subjects who receive at least one dose of study treatment and who have post treatment data for any

efficacy endpoint in the corresponding period will be included in the efficacy analysis for that endpoint.

PK Analysis: For each of initial 6-month period and the extension period, all subjects who receive at least one dose of study treatment in this study and have any post-treatment PK information in the corresponding period will be included in the analysis.

Imaging Assessment Analysis: For each of initial 6-month period and the extension period, all subjects who receive at least one dose of study treatment and who have post-treatment data for any imaging assessment endpoint in the corresponding period will be included in the analysis for that endpoint.

Biomarker Analysis: For each of initial 6-month period and the extension period, all subjects who receive at least one dose of study treatment in this study and have any post-treatment biomarker assessment in the corresponding period will be included in the analysis.

13.7 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/EC must be sought, and the Investigator should inform BioMarin and the full IRB/EC within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/EC 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/EC 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/EC, 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.

14 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 and PK of subjects in the study. The DMC will include independent experts and key opinion leaders in fields, which may include, but not limited to: ACH, natriuretic peptides, bone growth, cardiology, radiology, clinical pharmacology, and biostatistics. The DMC will make recommendations for stopping or continuing the study on a subject level and/or on a cohort level per the pre-specified stopping criteria. The DMC may also provide recommendations for dose modifications as needed for each cohort.

15 COMPENSATION, INSURANCE AND INDEMNITY

There will be no monetary compensation provided to subjects for their participation in this study. BioMarin is responsible for all study participation expenses, including tests, procedures, and treatments. In addition, BioMarin may reimburse the cost of travel for study-related visits after EC approval. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems that are not part of this protocol regardless of their relationship to the subject's disease. Costs associated with hospitalizations, tests, and treatments should be billed and collected in the way that such costs would be customarily billed and collected.

The Investigator should contact BioMarin immediately upon notification that a study subject has an injury related to the study treatment or to the procedures or assessments 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 contact information if they require further information about or 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 study treatment or study assessments or procedures if these costs are not covered by health insurance or another third party that customarily would pay 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.

16 CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic CRFs will be provided for each subject. The Investigator must review and electronically sign the completed CRF casebook to verify its accuracy.

CRFs must be completed using a web–based application that has been developed for the study and has been validated. Study site personnel or designee will be trained on the application and will enter the clinical data from source documentation. 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 Pharmaceutical policy is that study data on the CRFs 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.

A CRA designated by BioMarin will compare the CRFs with the original source documents at the study site and will evaluate them for completeness and accuracy before designating them as “Source Data Verified” (SDV). 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 CRF casebook can be locked, data fields must be source data verified and queries closed. Refer to the Study Monitoring Plan for details on which fields must be source data verified. The Investigator will then electronically sign the casebook, specifying that the information on the CRFs is accurate and complete. The Data Manager (or designee) will then set the status of the forms, visits, and the entire casebook to Locked. Upon completion of the

CSR, an electronic copy of each site's casebooks will be copied to a compact disk (CD) and will be sent to each site for retention with other study documents.

17 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 Pharmaceutical 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 audit 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.

18 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 (e.g., 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.

19 USE OF INFORMATION AND PUBLICATION

BioMarin recognizes the importance of communicating medical study data and therefore encourages their publication 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 institution of the Investigator.

20 REFERENCES

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21 INVESTIGATOR RESPONSIBILITES

21.1 Conduct of Study and Protection of Human Patients

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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 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 patients or others are reported to the IRB/EC. Additionally, he or she will not make any changes in the research without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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.

22 SIGNATURE PAGE

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

Protocol Number: 111-202

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:

DocuSigned by:

[redacted]

22-Aug-2016 | 9:59 AM PDT

S[redacted] Date

Printed Name: [redacted] MD PhD