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

NCT Number: NCT03583697

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 08 February 2019

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months
Protocol Number:	111-206
Active Investigational Product:	BMN 111 (modified rhCNP)
IND	111299
European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2016-003826-18
Indication:	Achondroplasia
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 2
Sponsor's Responsible Medical Monitor:	PI , MD, PhD PI BioMarin Pharmaceutical Inc. 10 Bloomsbury Way London WC1A 2SL
Study Design:	Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH
Treatment Duration	52 weeks
Duration of Subject Participation:	60 weeks for Cohorts 1 and 2 (screening, treatment, follow-up). Subjects in Cohort 3 who enter the study for a 12-week observational period will participate for approximately 70 weeks (screening, observational period, treatment, follow-up)
Dose:	15 µg/kg BMN 111 or placebo daily, subject to adjustment per protocol
Study Population:	Children 0 to < 60 months old with achondroplasia
Date of Original Protocol:	06 December 2017

2 SYNOPSIS

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

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

PROTOCOL NUMBER: 111-206

STUDY SITES: Approximately 10-15 sites worldwide

PHASE OF DEVELOPMENT: Phase 2

STUDY RATIONALE:

BMN 111 is a recombinant CNP analogue that has been engineered to resist degradation by NEP, allowing for a longer half-life.

The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ (TD) model (Lorget, 2012), and a milder [Ach] /+ (Ach) model. These included studies in 7-day old TD mice given BMN 111 daily by SC administration for up to 20 days and a study in 3-week old Ach mice given BMN 111 daily by SC administration for 5 weeks. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. In wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels (Wendt, 2015). Additionally, the potential effect of age on BMN 111 PK was evaluated in normal rats aged between 7 days and 12-13 weeks.

Infants and young children with ACH have a high incidence of medical complications and currently there is no approved pharmacological therapy for ACH in the US or EU. The most severe complication, cervicomedullary compression (CMC), occurs in a subset of subjects with ACH due to abnormal endochondral bone growth and narrowing of the foramen magnum (White, 2016). CMC has been linked to serious respiratory and neurological complications including hypotonia, apnea, ataxia, developmental delay, and respiratory arrest associated with sudden death (Mukherjee, 2014). Foramen magnum decompression surgery is currently the only treatment for this condition.

Sleep apnea has also been extensively described in ACH, and sleep-disordered breathing may affect up to 85% of all children with ACH (Ireland, 2012). This is thought to be due to midface hypoplasia, relative adenotonsillar hypertrophy, and potential posterior cranial fossa compression secondary to abnormal endochondral bone growth. Sleep apnea in ACH not only results in the need for surgical intervention, but has also been linked to sudden death in rare cases (Pauli, 1984).

Similarly, the dysregulation of endochondral bone growth in ACH leads to other medical

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complications which are prevalent in this subject population, such as the following:

- Spinal stenosis, kyphosis, and lordosis (secondary to altered growth plate ossification in the vertebrae and narrowing of the interpedicular distances) (Shirley, 2009)
- Developmental delay of gross motor and ambulatory skills (associated with proximal limb shortening, macrocephaly, and hypotonia) (Ireland, 2010)
- Delayed functional skills and increased need for caregiver assistance (eg, eating, bladder management, bowel management, transfer to chair, climbing stairs) (Ireland, 2011)

Thus, BMN 111 may provide greater benefit when children begin treatment at a younger age, as earlier initiation of treatment allows a longer time window to improve growth and potential to improve medical complications of achondroplasia. This study (111-206) is being conducted to assess safety and the potential benefit of BMN 111 in infants and young children.

BMN 111 was first tested in humans in Study 111-101, a Phase 1 double-blinded, placebo-controlled clinical trial of the safety and tolerability of BMN 111 in healthy adult male volunteers without ACH. Part 1 examined a series of single subcutaneous doses (5 µg/kg, 10 µg/kg and 15 µg/kg), and Part 2 included 10 days of either fixed dosing or dose escalation (0.5 µg/kg to 8 µg/kg). BMN 111 was generally well tolerated at all doses. As expected, mild, transient, self-limited hypotension was reported (refer to current Investigators Brochure for additional information). Following SC administration, BMN 111 was rapidly absorbed with maximal plasma concentrations achieved in less than 30 minutes. BMN 111 was rapidly cleared from the plasma with a mean $t_{1/2}$ ranging from 40 to 55 minutes across dose levels. BMN 111 exposure (C_{max} and AUC_{0-t}) generally increased greater than proportional to the increase in dose across the 2.5-to-15-µg/kg dose range. Exposure following multiple dosing was found to be similar to exposure following single doses, indicating no apparent accumulation or time-dependence with once-daily SC administration.

Study 111-202, the second clinical trial in humans and the first in children with ACH, is an ongoing Phase 2, open-label, sequential-cohort, dose-escalation study that assesses daily SC BMN 111 in pediatric subjects with ACH aged 5-14 years with doses ranging from 2.5 µg/kg to 30 µg/kg. The primary objective of Study 111-202 is to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months; the secondary objectives are to determine change from baseline in annualized growth velocity (AGV), growth parameters, body proportions, and evaluate the pharmacokinetics (PK) of BMN 111 in children with ACH.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at the doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated (refer to current Investigator's Brochure for specific details). One subject (30 µg/kg) in 111-202 withdrew due to an AE. The subject developed non-serious, asymptomatic Grade 1 intermittent Wolff-Parkinson-

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White pattern, which was discovered on a routine day 10-study monitoring ECG. The most common AEs across all cohorts were injection site reactions, asymptomatic hypotension, headache, and nasopharyngitis. Based on previous experience of the ongoing Phase 2 clinical trial, including the 24-month data cut at 15 µg/kg, injection site reactions have been identified as risks associated with BMN 111 injections. The majority of hypotension events were grade 1 and reported in the setting of routine BP measurement. All reported events of hypotension were transient and resolved without medical intervention. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

Analysis of efficacy data from the 6-month initial phase of Study 111-202 showed that subjects treated with BMN 111 for 6 months at doses ranging from 2.5-15 µg/kg daily had a dose-dependent improvement in AGV, with ~50% improvement in AGV seen at the 15 µg/kg dose. The data from Cohort 4 (30 µg/kg) show an apparent greater than dose-proportional increase in BMN 111 plasma exposure (C_{max} and AUC_{0-t}), 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).

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are 0 to < 60 months old. This 52-week study will enable assessment of BMN 111 efficacy and safety, tolerability, pharmacodynamics biomarkers, and PK in this population. Additional exploratory endpoints pertaining to medical complications of ACH will also be evaluated.

Efficacy/toxicity studies have been conducted in neonatal and very young animals (7-day postpartum mouse and rat) in both a disease (TD mouse) and non-disease (rat) model. Given that this is the first study in infants and young children, an age-based cohort study design is used to assess safety and PK in young children (Cohort 1, ≥ 24 to < 60 months) prior to dosing toddlers (Cohort 2, ≥ 6 to < 24 months) and infants (Cohort 3, 0 to < 6 months). PK will be monitored and evaluated; Day 1 PK data from the sentinel subjects will inform dose selection modification for the sentinel subjects and for the rest of the cohort to target the observed exposure of the 15-µg/kg dose group in Study 111-202. Safety, efficacy and PK data from Study 111-202, a Phase 2 study in children with ACH, where a dose of 15 µg/kg has been and continues to be studied, are expected to be the most relevant, and translatable to this study (111-206).

OBJECTIVES:

The primary objectives of the study are to:

- Evaluate the safety and tolerability of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate the effect of BMN 111 on change from baseline in length/height Z-score

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The secondary objectives of the study are to:

- Evaluate the effect of BMN 111 on AGV throughout the 52 weeks of the study
- Evaluate the effect of BMN 111 on bone morphology/quality by x-ray and dual x-ray absorptiometry (DXA)
- Evaluate the PK of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait from medical history
- Evaluate the effect of BMN 111 on developmental/functional/QOL status (Bayley-III, WeeFIM, Child Behavior Checklist [CBCL], ITQOL
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of BMN 111 on bone metabolism and BMN 111 pharmacodynamic biomarkers

The exploratory objectives of the study are to:

- Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower segment body ratio
- Evaluate the effect of BMN 111 on sleep apnea
- Document physical and phenotypic changes with clinical photography (optional)
- Evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

STUDY DESIGN AND PLAN:

This study, 111-206, is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH.

Study 111-901 is an ongoing study to collect serial growth measurements on pediatric subjects with ACH who are being considered for subsequent enrollment in future BioMarin studies. Subjects age≥3 months to < 60 months old who have documented ACH confirmed by genetic testing, at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry, and who meet the study eligibility criteria will participate in Study 111-206. Eligible subjects ranging from 0 months to <3 months old may enroll directly into 111-206 and have a minimum of 3 months of pre-treatment observation prior to commencing treatment.

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

The primary objectives of this study are to assess the safety and tolerability of daily SC BMN 111 administered to infants and young children with ACH, and evaluate the effect of BMN 111 on length/height Z-score. Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive BMN 111, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who will be under observation or receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

If subjects who enroll in Cohort 3 are not able to begin treatment by <6 months of age, they will continue in the pretreatment period for another 3 months before enrolling in Cohort 2 to fulfill the pretreatment requirement for Cohort 2.

Sentinel subjects from each cohort will be enrolled, treated with BMN 111, and studied for short-term safety and PK data, after which subjects will be randomized to receive BMN 111 or placebo SC daily (1:1 ratio) for up to 52 weeks.

At the start of the study, three sentinel subjects will be enrolled and monitored in Cohort 1. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data review, the weight-based dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 1 (≥ 27 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort (Cohort 2) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 2. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and

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PK data, the remainder of Cohort 2 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the youngest cohort (Cohort 3) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 3. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 3 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio).

Cohort 3 subjects must have a minimum of 3 months of observation prior to commencement of treatment. These subjects will have the option to enroll in either 111-901 or 111-206, depending on age at enrollment:

- Infants ≥ 3 months and <6 months old (≥ 13 weeks and <26 weeks) will enroll in 111-901 for a 6-month period of pretreatment growth assessment prior to enrollment in 111-206 for treatment in Cohort 2.
- Infants between birth and < 3 months old (0 weeks and < 13 weeks) will enroll into 111-206 with a 3-month observational period prior to treatment.

Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in all treatment groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term.

For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

Data Monitoring Committee (DMC)

In addition to safety and PK 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. After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort will be opened and the 3 sentinel subjects will be enrolled.

The DMC will make recommendations for stopping or continuing the study on an individual subject level and/or on a cohort level per the pre-specified stopping criteria. Based on criteria outlined in the protocol, the DMC may also make endorsements for dose adjustments if needed.

Please see DMC Charter for further details.

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Individual Subject Stopping Criteria

For individual subjects treated with BMN 111, DMC will be informed if any of the following individual subject stopping criteria should occur. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the individual subject will be considered.

- Any treatment-emergent adverse event (AE) assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (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
- Clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec
- Clinically significant new or worsening signs of cervicomedullary compression as determined by the Investigator and in consultation with Sponsor medical monitor and neurosurgical specialist (if needed)
- Adverse findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as determined by the Investigator and in consultation with Sponsor Medical Monitor and orthopedic specialist (if needed)

If the subject meets any stopping criterion, 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 is not clinically indicated, other options that may be considered include:

- Permanent treatment discontinuation (with an option of ongoing assessment in the study)

Cohort Stopping Criteria

For each cohort, a DMC review will be conducted if any of the following cohort stopping criteria occur in subjects treated with BMN 111. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the cohort(s) will be considered and the impact on all other age cohorts will be assessed.

- Any treatment-emergent AE assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor

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- Any two subjects have a treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any two subjects cohort have a Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Any two subjects have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec
- Any two subjects have adverse 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)

Dose Adjustments

Analysis of available PK data from studies 111-101 and 111-202 indicated that differences in subject body weight did not directly translate to differences in total body clearance of BMN 111. The same weight-based dose in the pediatric population of Study 111-202 (5-12 years old) yielded lower exposure (C_{max} and AUC) than that characterized in the adult population of Study 111-101. Therefore, the same weight-based dose in the young pediatric population in this study may yield exposure less than the target exposure range characterized to be safe and effective in Study 111-202 at the 15-µg/kg dose. Since this is the first experience with BMN 111 in this young pediatric population, it is also possible the exposure at 15 µg/kg could be greater than the target exposure range, and dose adjustment may be warranted. Thus, an option for adjustment of the weight-based dose is provided to ensure that the appropriate target exposure for safety and efficacy is reached for the young subjects in this study.

The need for dose adjustment will be evaluated as follows: three sentinel subjects in Cohort 1 will receive an initial dose of 15 µg/kg. After all three sentinel subjects reach Day 8, a review will occur to evaluate all available safety and PK data (at minimum). If the criteria for dose adjustment are met, the three sentinel subjects will be started on the new adjusted dose at their next scheduled visit, and vital signs will be obtained for at least 4 hours post-dose.

The remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. After the third sentinel subject reaches day 30 post dose adjustment, a DMC review will occur to evaluate all safety and PK data and, upon endorsement, the three sentinel subjects from the next younger cohort will be enrolled starting at the new adjusted dose. The three sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment.

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Safety and Efficacy Monitoring

Each treated subject will have expanded outpatient safety monitoring for a minimum of 3 days of dosing, during which they will be closely observed and non-invasive hemodynamic monitoring will be conducted for at least 4-8 hours post-dosing. Because younger children may not be able to verbalize complaints of dizziness or lightheadedness that are potentially associated with hypotension, study personnel and caregivers will be trained to recognize the signs of hypotension in this population, which may include tachycardia, pallor, diaphoresis, lethargy, delayed capillary refill, and poor feeding. Appropriate rigorous training will be required for parents and caregivers prior to daily injections at home. Training includes the storage, reconstitution, and administration of BMN 111, as well as documentation/reporting of AEs and vigilance for signs of hypotension.

It is generally expected that after subjects are tolerating the drug well and specified criteria have been met, caregivers will begin administering study drug. Home health care is not required at any point but may be provided if the caregiver is unable or unavailable to administer the study drug. A Home Healthcare nurse will train the caregiver(s) if training has not been completed by the Day 3 visit. A phone call by the study staff member to the caregiver will be required weekly for 6 months and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. If the caregiver cannot be contacted by phone after two attempts, contact can be made via email.

Safety will be evaluated by the incidence of AEs, serious AEs (SAEs), laboratory test results (urinalysis, chemistry, and hematology), vital signs, physical examination, ECG and echocardiogram, hip clinical assessment, and anti-BMN 111 immunogenicity assessments. Clinical laboratory tests, PK, immunogenicity and blood biomarker assessments will be limited to the minimum necessary for evaluation of safety and efficacy in order to minimize blood volume in the pediatric population.

Efficacy will be assessed by change from baseline in AGV and length/height Z-score. Exploratory assessments will include change from baseline in growth parameters and body proportions by anthropometry. X-rays will be performed of the lower extremities and spine to evaluate for changes in bone morphology, quality, and growth. An MRI will be performed to assess the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions. A board-certified, fellowship-trained (or equivalent) pediatric anesthesiologist will administer anesthesia during MRI measurements in the event that the subject is unable to remain still for the duration of the scan. Sleep studies will be conducted to evaluate sleep apnea. Additional assessments will be conducted to evaluate changes from baseline in bone metabolism and BMN111 pharmacodynamic biomarkers, and developmental/functional status.

NUMBER OF SUBJECTS PLANNED: Approximately 70 subjects, including at least 30 subjects in Cohort 1, at least 20 subjects in Cohort 2, and at least 20 subjects in Cohort 3.

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DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Diagnosis of ACH, confirmed by genetic testing. If subjects had previous genetic testing, subjects must have a lab report from a certified laboratory with the study specific mutation documented.
2. Age 0 to < 60 months, at study entry (Day 1)
3. Cohort 1 and 2 subjects must have at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry, and have one documented measurement of height/body length a minimum of 6 months (+/- 10 days) prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrollment in Study 111-901 or (2) via enrollment in this Study 111-206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment.
4. Parent(s) or guardian(s) (and the subjects themselves, if required by local regulations or ethics committee) 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
5. Willing and able to perform all study procedures as physically possible
6. Parent(s) or caregiver(s) are willing to administer daily injections to the subjects and complete the required training

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

1. Have hypochondroplasia or short-stature condition other than achondroplasia (e.g., trisomy 21, pseudoachondroplasia, etc.)
2. Subject weighs < 5.0 kg (Cohorts 1 and 2) or < 4.0 kg (Cohort 3)
3. Have any of the following:
   - Hypothyroidism or hyperthyroidism
   - Insulin-requiring diabetes mellitus
   - Autoimmune inflammatory disease (including celiac disease, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, etc.)
   - Inflammatory bowel disease
   - Autonomic neuropathy
4. Have a history of any of the following:
   - Renal insufficiency defined as serum creatinine > 2 mg/dL
   - Chronic anemia or Hgb < 10.0 g/dL (based on screening clinical laboratory testing)
   - Baseline systolic blood pressure (BP) below age and gender specified normal range or

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recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms e.g., dizziness, fainting) or recurrent symptomatic orthostatic hypotension

- Cardiac or vascular disease, including the following
  - Cardiac dysfunction (abnormal echocardiogram determined to be clinically significant by PI and medical monitor) at Screening Visit
  - Hypertrophic cardiomyopathy
  - Pulmonary hypertension
  - Congenital heart disease with ongoing cardiac dysfunction
  - Cerebrovascular disease
  - Aortic insufficiency or other clinically significant valvular dysfunction
  - Clinically significant atrial or ventricular arrhythmias

5. Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F >450 msec on screening ECG
6. Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator based on the following assessments:
   - Physical exam (eg, neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins)
   - Polysomnography (eg, severe central sleep apnea)
   - MRI indicating presence of severe CMC or spinal cord damage
7. Have an unstable medical condition likely to require surgical intervention in the next 6 months, or planned spine or long-bone surgery (i.e., surgery involving significant disruption of bone cortex) during the study period
8. Have documented uncorrected Vitamin D deficiency: 25(OH)D ≤15 ng/mL (37.5 nmol/L)
9. Require any other investigational product prior to completion of the study period
10. Have received another investigational product or investigational medical device within 30 days prior to the Screening visit
11. Have used any other investigational product or investigational medical device for the treatment of achondroplasia or short stature at any time
12. Require current chronic therapy with antihypertensive medication or any medication that, in the investigator's judgment, may compromise the safety or ability of the subject to participate in this clinical study
13. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (> 3 months) at any time
14. Have had regular long-term treatment (>1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the 12 months prior to

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screening

15. Have ever had spine or long-bone surgery (ie, surgery involving disruption of bone cortex) or have ever had bone-related surgery with chronic complications
16. Have ever had limb-lengthening surgery or plan to have limb-lengthening surgery during the study period
17. Have had a fracture of the long bones or spine within 6 months prior to screening
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin greater than upper limit of normal at screening (except for subjects with a known history of Gilberts or newborns entering screening in Cohort 3)
19. Have evidence of severe untreated sleep apnea; or have newly initiated sleep apnea treatment (eg, CPAP or sleep apnea-mitigating surgery) in the 2 months prior to screening
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 history of hip surgery or severe hip dysplasia
23. Have a history of clinically significant hip injury in the 30 days prior to screening
24. Have a history of slipped capital femoral epiphysis or avascular necrosis of the femoral head
25. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the Investigator
26. 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
27. Have any concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, for any reason

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 a 0.8-mg or 2-mg lyophilized, preservative-free, white-to-yellow powder for reconstitution with either a sterile diluent or sterile water for injection. The reconstituted solution is colorless to yellow and contains 0.8 mg/mL to 2 mg/mL of BMN 111, as well as citric acid, sodium citrate, trehalose, mannitol, methionine, polysorbate 80, and sterile water for injection. The target pH of the reconstituted solution is 5.5. Sterile water for injection will be commercially sourced and sterile diluent solution containing all of the above excipients will be supplied for reconstitution. All reconstitution and dose preparation steps will be performed as indicated in the BMN 111 Injection Guide and Injection video.

BMN 111 will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on

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

subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic.

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

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

Placebo will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic.

DURATION OF TREATMENT: Up to 52 weeks

CRITERIA FOR EVALUATION:

Safety: The following safety outcome measurements will be assessed:

- Incidence of AEs and SAEs
- Vital signs (heart rate, blood pressure, respiratory rate, and temperature)
- Physical examination (including neurological assessment)
- Hip clinical assessment
- Laboratory test results (urinalysis, chemistry, hematology)
- Electrocardiogram (ECG)
- Echocardiogram
- Anti-BMN 111 immunogenicity assessments
- Cortisol levels
- Prolactin levels

Efficacy: The following efficacy outcome measurements will be assessed:

- Change from baseline in AGV
- Change from baseline in length/height Z-score

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 ($AUC_{0-\infty}$)

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- Area under the plasma concentration-time curve from 0 to the time of last measurable concentration (AUC_{0-t})
- Maximum plasma concentration (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 (Vz/F)

Drug accumulation after repeat-dose administration will also be evaluated. PK parameters at Week 13, 26, 39 and 52 will be compared to Day 1. The impact of immunogenicity (if present) on PK will also be evaluated.

Bone metabolism and BMN 111 pharmacodynamic biomarkers:

- Changes in bone and collagen metabolism and BMN 111 activity will be assessed.

Clinical outcome assessments:

- Bayley-III
- WeeFIM
- CBCL
- ITQOL

Exploratory: The following exploratory measurements will be assessed:

- Upper:lower body segment ratio
- Imaging assessments (X-rays of the spine and lower extremities)
- MRI to define skull and brain morphology (including dimensions of foramen magnum, ventricular and brain parenchymal dimensions)
- Sleep study
- Clinical photography (optional)

STATISTICAL METHODS:

Sample Size Determination: Approximately 70 subjects age 0 to < 60 months at study entry will participate in this study. No formal sample size calculations were performed. The number of subjects is considered appropriate to evaluate the safety and efficacy of BMN 111 in the target population.

Safety Analysis: All subjects who receive at least one dose of study treatment or who are randomized to the placebo-control group in this study will be included in the safety analysis. The safety analysis will be descriptive.

All AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities

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(MedDRA) to assign system organ class and preferred term classification to event and disease, based on the original terms entered on the eCRF. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment as assessed by the investigator, seriousness, 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, echocardiogram, hip clinical assessment, and concomitant medication data will also be summarized descriptively. Data summaries will be presented by treatment group (when applicable) for each cohort and overall. All safety results will be listed.

Efficacy Analysis:

All randomized subjects who receive at least one dose of study treatment or placebo in the study will be included in the efficacy analysis.

Efficacy variables, including AGV (based on length/height) and length/height Z-score according to normal reference standards (not ACH), along with their change from baseline will be summarized by treatment group and cohort. Comparisons between treatment groups by cohort on these variables will be carried out where appropriate. Statistical comparisons will be considered descriptive. 95% CIs will be provided along with p values for treatment group comparisons.

Sentinel subjects will be summarized apart for both efficacy and safety.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

°C	degree Celsius
ACE	angiotensin-converting enzyme
Ach	Fgfr3G380R achondroplasia mouse model
ACH	achondroplasia
ADL	Activity of Daily Living
ADR	adverse drug reaction
AE	adverse event
AGV	annualized growth velocity
ALT	alanine aminotransaminase
ANP	atrial natriuretic peptide
AP	anterior-posterior
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMC	bone mineral content
BMD	bone mineral density
BNP	B-type Natriuretic Peptide
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
C_{max}	maximum observed plasma concentration
CBCL	Child Behavior Checklist
CNP	C-type natriuretic peptide
CNP53	C-type natriuretic peptide (53 amino acids in length)
CRA	clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DCF	data clarification form
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FGF	fibroblast growth factor
G380R	substitution in the transmembrane domain of the FGFR3 receptor at position 380
GCP	Good Clinical Practice

HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRQOL	health-related quality of life
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICH E6 [R2]	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	Independent ethics committee
IgE	immunoglobulin E
IND	Investigational New Drug (application)
IP	investigational product
IRB	institutional review board
ITQOL	Infant Toddler Quality of Life questionnaire
LV	left ventricular
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
msec	millisecond
NAb	neutralizing antibodies
NEP	neutral endopeptidase
NP	natriuretic peptide
NPR-B	natriuretic peptide receptor type B
PA	posterior-anterior
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
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
REB	research ethics board
rhCNP	recombinant C-type natriuretic peptide
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOI	Statement of Investigator Form
$t_{1/2}$	elimination half-life
TAb	total antibody

Tmax	time to reach C_{max}
ULN	upper limit of normal
US	United States
WeeFIM	Functional independence measure for children
WFI	water for injection
µg/kg	microgram/kilogram

Definition of Terms:

Investigational Product (IP):

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6] (R2)]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated for subjects who do not speak the local language at 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/IEC/REB confirming unconditional approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the Investigator and copies are received at BioMarin or its designee. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the study are made to the IRB/IEC/REB and BioMarin by the Investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

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

This study will be conducted in accordance with the following:

- European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, for studies conducted within any European country
- 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) or E6(R2) (ICH E6R2) if adopted
- The ethical principles established by the Declaration of Helsinki

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

5.3 Subject Information and Informed Consent

A properly written and executed informed consent form (ICF), in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, 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/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF (minor assent form and parental ICF for studies involving minors), and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

Subjects under the age of 18 years will provide written assent (if required), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects. The Investigator will provide copies of the signed ICF to each subject (or the legally authorized representative of the subject) and will maintain the original in the record file of the subject.

6 INVESTIGATORS AND STUDY ADMINSTIRATIVE 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 Statement of Investigator (SOI) form. A US Food and Drug Administration (FDA) Form FDA 1572 serves as an acceptable SOI form. If Form FDA 1572 may not be used in a particular region, the Investigator must provide a fully executed SOI on the form provided by the Sponsor. All Investigators and Sub-Investigators must be listed on Form FDA 1672 or its equivalent SOI. Financial Disclosure Forms must also be completed for all Investigators and Sub-Investigators listed on the Form FDA 1572 or SOI who will be directly involved in the treatment or evaluation of subjects in this study.

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

In multicenter studies, 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.

7 INTRODUCTION

BMN 111 is a proposed pharmacologic 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) The average adult heights for men and women with ACH are 131 cm and 124 cm, respectively (NIH, Genetics Home Reference, 2012). Characteristic features include long and narrow trunk, a large head with frontal bossing, hypoplasia of the mid-face, bowed legs and stenosis of the foramen and spinal canals that can be life-threatening. Foramen magnum stenosis can lead to cervicomedullary compression in infants with complications including hydrocephalus, hypotonia, respiratory insufficiency, apnea, cyanotic episodes, feeding problems, quadriparesis, and sudden death.

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

ACH is caused by a gain-of-function mutation in 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.

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

CNP is a member of the natriuretic peptide (NP) family that includes Atrial Natriuretic Peptide (ANP) and B-type Natriuretic Peptide (BNP). These peptides are structurally related but are distinct paracrine/autocrine (CNP) or endocrine (ANP and BNP) factors that regulate

the cardiovascular (CV), skeletal, nervous, reproductive and other systems. Synthetic analogs of ANP (anaritide and carperitide) and BNP (nesiritide) have been investigated as potential therapies for the treatment of decompensated heart failure and cardiovascular-related diseases.

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

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

7.1 Nonclinical Studies

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

BMN 111-related adverse findings in nonclinical species (mice, rats, cynomolgus monkeys) were limited to the known mechanism of action of CNP on the growth plate and vasculature. Reversible subcutaneous injection site reactions were reported, including injection site discoloration and microscopic findings of perivascular mononuclear cell infiltrates that were seen with slightly higher incidence and severity in BMN 111-treated rats and monkeys compared to the vehicle control. Adverse skeletal changes associated with exaggerated growth were seen in normal nonclinical species with open growth plates, and were dose-, exposure- and time-dependent. Decreases in blood pressure and compensatory increases in heart rate were detected in monkeys across multiple studies, with overt CV-related clinical signs observed in some animals at doses $\geq$ 236 µg/kg. These overt clinical signs consisted of transient, short and repeated bouts of sternal or lateral recumbency and/or reduced motor

activity, typically within 1-hour post-dose administration. Additional detailed information about nonclinical studies of BMN 111 is provided in the current version of the Investigator's Brochure supplied by BioMarin.

7.2 Previous Clinical Studies

7.2.1 Study 111-101

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

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

The PK parameters for BMN 111 were obtained from Part 1 of the study and from the first dose on Day 1 of the multiple dose study in Part 2. The results demonstrate that BMN 111 was rapidly absorbed in human, reaching a mean time to peak concentration (T_{max}) between 15-26 minutes. After reaching maximal plasma concentrations, BMN 111 levels rapidly declined, with a $t_{1/2}$ of 40-55 minutes. Mean plasma concentration-time profiles indicate that exposure increased with dose from 2.5 to 15 µg/kg. The corresponding increases in plasma C_{max} and area under the curve (AUC) exposure parameters were greater than dose proportional. The increase in C_{max} with dose was linear over the dose range evaluated. In Part 2, with multiple dosing at 5 µg/kg for 10 days, the plasma concentration-time curves obtained on each of the three sampling days were nearly superimposable. Comparison of PK exposure parameters for AUC and C_{max} indicate that C_{max} is unchanged and AUC is

increased slightly by +33% over Day 1. Overall the results indicate that changes in BMN 111 exposure are minimal with repeat dosing out to 10 days.

7.3 Ongoing Clinical Studies

7.3.1 Study 111-901

Study 111-901 is a multicenter, multinational study to collect serial growth measurements on pediatric subjects with ACH who are being considered for subsequent enrollment in future studies sponsored by BioMarin. To obtain accurate baseline measurements, at least 6 months of growth data are collected.

Data gathered from this study are used to characterize baseline growth data in children or infants (defined as children < 2 years of age) who may subsequently be enrolled in future studies sponsored by BioMarin, and may also be used to establish historical control cohort for use in other BioMarin-sponsored studies, when appropriate. For that reason, data related to ACH symptoms, tests, and interventions are collected.

7.3.2 Study 111-202

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

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

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

For longer term follow up data from the 202 study, please refer to the current Investigator Brochure supplied by BioMarin.

7.3.3 Study 111-205

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

7.3.4 Study 111-301

Study 111-301 is an ongoing Phase 3, double-blind, placebo-controlled multicenter study to further characterize and confirm efficacy and safety of BMN 111 at 15 µg/kg in a 58-week study (up to 4 weeks of screening, 52 weeks of treatment, plus an additional 2 weeks of safety follow up). The study assesses the effect of daily BMN 111 administration on change from baseline in AGV, height, and body proportions in subjects treated with BMN 111 compared with control subjects in the placebo group; and further characterizes safety and tolerability of BMN 111 in children with ACH. Additional exploratory endpoints are being examined to determine the effect of BMN 111 on bone physiology and to assess quality of life and daily function of study subjects.

7.4 Study Rationale

BMN 111 is a recombinant CNP analogue that has been engineered to resist degradation by NEP, allowing for a longer half-life.

The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ (TD) model (Lorget, 2012), and a milder [Ach] /+ (Ach) model. These included studies in 7-day old TD mice given BMN 111 daily by SC administration for up to 20 days and a study in 3 week old Ach mice given BMN 111 daily by SC administration for 5 weeks. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. In wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels (Wendt, 2015). Additionally, the potential

effect of age on BMN 111 PK was evaluated in normal rats aged between 7 days and 12-13 weeks.

Infants and young children with ACH have a high incidence of medical complications and currently there is no approved pharmacological therapy for ACH in the US or EU. The most severe complication, cervicomedullary compression (CMC), occurs in a subset of subjects with ACH due to abnormal endochondral bone growth and narrowing of the foramen magnum (White, 2016). CMC has been linked to serious respiratory and neurological complications including hypotonia, apnea, ataxia, developmental delay, and respiratory arrest associated with sudden death (Mukherjee, 2014). Foramen magnum decompression surgery is currently the only treatment for this condition.

Sleep apnea has also been extensively described in ACH, and sleep-disordered breathing may affect up to 85% of all children with ACH (Ireland, 2012). This is thought to be due to midface hypoplasia, relative adenotonsillar hypertrophy, and potential posterior cranial fossa compression secondary to abnormal endochondral bone growth. Sleep apnea in ACH not only results in the need for surgical intervention, but has also been linked to sudden death in rare cases (Pauli, 1984).

Similarly, the dysregulation of endochondral bone growth in ACH leads to other medical complications which are prevalent in this subject population, such as the following:

- Spinal stenosis, kyphosis, and lordosis (secondary to altered growth plate ossification in the vertebrae and narrowing of the interpedicular distances) (Shirley, 2009)
- Developmental delay of gross motor and ambulatory skills (associated with proximal limb shortening, macrocephaly, and hypotonia) (Ireland, 2010)
- Delayed functional skills and increased need for caregiver assistance (eg, eating, bladder management, bowel management, transfer to chair, climbing stairs) (Ireland, 2011)

Thus, BMN 111 may provide greater benefit when children begin treatment at a younger age, as earlier initiation of treatment allows a longer time window to improve growth and potential to improve medical complications of achondroplasia. This study (111-206) is being conducted to assess safety and the potential benefit of BMN 111 in infants and young children.

BioMarin has engineered a CNP analog (BMN 111) that has a longer half-life than endogenous CNP, thereby allowing daily SC administration. Similar to CNP, BMN 111 activates NPR-B signaling with subsequent inhibition of FGFR3 downstream signaling, leading to the promotion of chondrocyte proliferation and differentiation and subsequent

increased endochondral bone formation. BMN 111 administration has been shown to promote endochondral bone formation at hemodynamically tolerated dose levels in both normal animals and mouse models of ACH reported (refer to current Investigator's Brochure for additional information).

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

Study 111-202 is an ongoing Phase 2, open-label, sequential cohort, dose escalation study that assesses daily SC administration of BMN 111 in pediatric subjects with ACH, in which the primary objective is to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months and includes secondary objectives consisting of determination of change from baseline in AGV, growth parameters, body proportions, and evaluation of the dose-exposure and PK profiles of BMN 111 in children with ACH.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 was generally well tolerated at all dose levels (refer to current Investigators Brochure for specific details).

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

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

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are age 0 to < 60 months. This 52-week study will enable assessment of BMN 111 safety, tolerability, pharmacodynamics biomarkers, and PK in this population, and also allow for examination of potential impact on efficacy endpoints. Additional exploratory endpoints pertaining to medical complications of ACH will also be evaluated.

7.5 Summary of Overall Risks and Benefits

7.5.1 Summary of Risks from Nonclinical Studies

Individuals in this study will be exposed to a recombinant analogue of human C-type natriuretic peptide (CNP). Based on the results of experimentation in animals, the most relevant potential toxicities relate to the expected pharmacological effects of exogenous CNP administration, including hemodynamic changes, skeletal overgrowth, and injection site reactions. Transient and sporadic decreases in blood pressure and compensating increases in heart rate occurred within the first hour post-dose in cynomolgus monkeys; the effects were mainly asymptomatic with a subset of animals given doses ≥ 236 µg/kg observed with symptomatic effects consisting of transient, short and repeated bouts of sternal or lateral recumbency and/or reduced motor activity. These hemodynamic effects can be monitored, but have the potential to be an acute dose-limiting factor in patients. Exaggerated appendicular bone responses to the drug included abnormally shaped femoral head, acetabular growth center/plate dysplasia and concomitant articular cartilage degeneration with clinical manifestations of restricted use of hips. Adverse skeletal changes associated with exaggerated growth were dose-, exposure- and time-dependent. Additional detailed information about risks identified in nonclinical studies of BMN 111 is provided in the current version of the Investigator's Brochure supplied by BioMarin.

7.5.2 Summary of Risks from Clinical Studies

7.5.2.1 Study 111-101

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

7.5.2.2 Ongoing Studies

Based on analysis of safety data from ongoing phase 2 and 3 studies, treatment with BMN 111 was generally well tolerated. Injection site reactions were the most common adverse events reported and are considered to be an identified risk. All injection site reactions events have been reported as non-serious, Grade 1 in severity, and transient. Hypotension and hypersensitivity reactions including development of BMN 111 antibodies are potential risks

associated with BMN 111 injections. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

7.5.3 Summary of Potential Benefits from Clinical Studies

For children with ACH who will receive BMN 111 as part of Study 111-206, potential benefits may include improvement of AGV rates such that their increase in growth velocity may approach that of children of average stature. Additional potential benefits may include improvement of the disproportionate growth as well as improvement in quality of life, activities of daily living, and medical complications of ACH. For example, improvement in height could have an impact on daily activity performance.

8 STUDY OBJECTIVES

The primary objectives of the study are to:

- Evaluate the safety and tolerability of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate the effect of BMN 111 on change from baseline in length/height Z-score

The secondary objectives of the study are to:

- Evaluate the effect of BMN 111 on AGV throughout the 52 weeks of the study
- Evaluate the effect of BMN 111 on bone morphology/quality by x-ray and dual x-ray absorptiometry (DXA)
- Evaluate the PK of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait from medical history
- Evaluate the effect of BMN 111 on developmental/functional/QOL status (Bayley-III, WeeFIM, Child Behavior Checklist [CBCL], ITQOL
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of BMN 111 on bone metabolism and BMN 111 pharmacodynamic biomarkers

The exploratory objectives of the study are to:

- Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower body segment ratio
- Evaluate the effect of BMN 111 on sleep apnea
- Document physical and phenotypic changes with clinical photography (optional)
- Evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH.

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

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

The primary objectives of this study are to assess the safety and tolerability of daily SC BMN 111 administered to infants and young children with ACH, and evaluate the effect of BMN 111 on Z-scores. Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive BMN 111, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 20 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

If subjects who enroll in Cohort 3 are not able to begin treatment by < 6 months of age, they will continue in the pretreatment period for another 3 months before enrolling in Cohort 2 to fulfill the pretreatment requirement for Cohort 2.

Sentinel subjects from each cohort will be enrolled and studied for short-term safety and PK data, after which subjects in all 3 cohorts will be randomized to receive BMN 111 or placebo SC daily (1:1 ratio) for up to 52 weeks. At the start of the study, 3 sentinel subjects will be enrolled and monitored in Cohort 1. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 1 (≥ 27 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort (Cohort 2) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 2. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 2 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the youngest cohort (Cohort 3) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 3. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 3 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio).

Cohort 3 subjects must have a minimum of 3 months of observation prior to commencement of treatment. These subjects will have the option to enroll in either 111-901 or 111-206, depending on age at enrollment:

- Infants ≥ 3 months and < 6 months old (≥ 13 weeks and < 26 weeks) will enroll in 111 901 for a 6-month period of pretreatment growth assessment prior to enrollment in 111 206 for treatment in Cohort 2.
- Infants between birth and < 3 months old (0 weeks and < 13 weeks) will enroll into 111 206 with a 3-month observational period prior to treatment.

Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

Each treated subject will have expanded outpatient safety monitoring for a minimum of 3 days of dosing, during which they will be closely observed and non-invasive hemodynamic monitoring will be conducted for at least 4-8 hours post-dosing. Because younger children may not be able to verbalize complaints of dizziness or lightheadedness that are potentially associated with hypotension, study personnel and caregivers will be trained to recognize the signs of hypotension in this population, which may include tachycardia, pallor, diaphoresis, lethargy, delayed capillary refill, and poor feeding. Appropriate rigorous training will be required for parents and caregivers prior to daily injections at home. Training includes the storage, reconstitution, and administration of BMN 111, as well as documentation/reporting of AEs and vigilance for signs of hypotension.

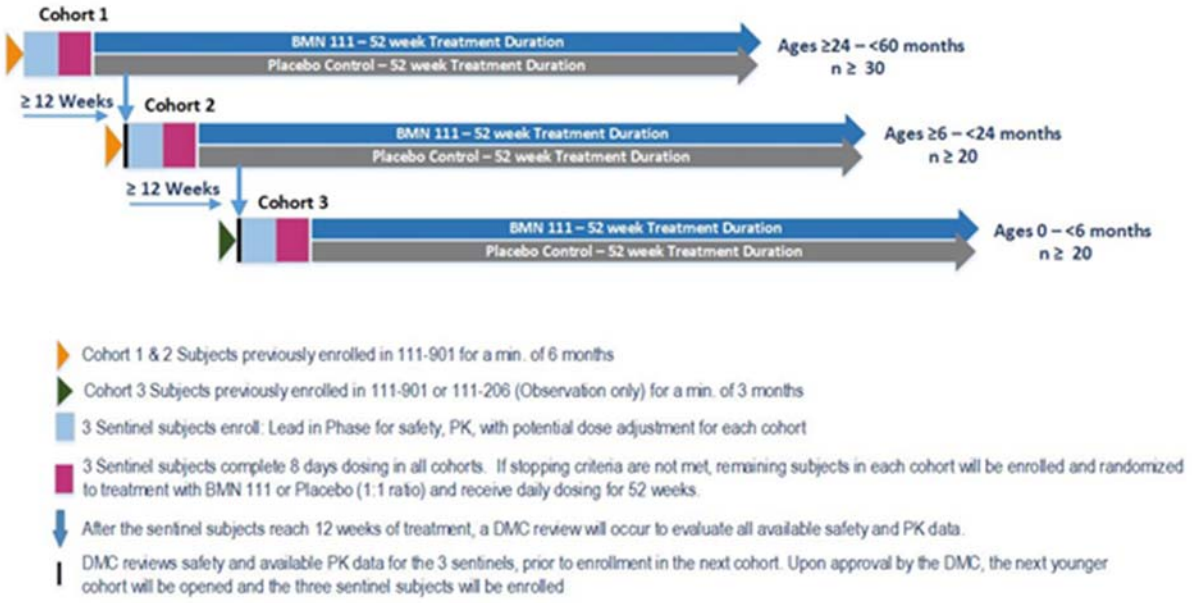
It is generally expected that after subjects are tolerating the drug well and specified criteria have been met, caregivers will begin administering study drug. Home health care is not required at any point but may be provided if the caregiver is unable or unavailable to administer the study drug. A Home Healthcare nurse will train the caregiver(s) if training has not been completed by the Day 3 visit. A phone call by the study staff member to the caregiver will be required weekly for 6 months and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. If the caregiver cannot be contacted by phone after two attempts, contact can be made via email.

Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in all treatments groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term. For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

A summary of events and assessments are provided by visit in Table 9.1.1 and Table 9.1.2.

For a discussion of efficacy assessments, see Section 9.11.2 and Section 9.11.3; exploratory efficacy assessments, Section 9.11.4; safety assessments, Section 9.11.6; and PK variables, Section 9.11.5. The 111-206 study design is presented in Figure 9.1.1.

Figure 9.1.1: Study Design



Cohort 1 & 2 Subjects previously enrolled in 111-901 for a min. of 6 months

Cohort 3 Subjects previously enrolled in 111-901 or 111-206 (Observation only) for a min. of 3 months

3 Sentinel subjects enroll: Lead in Phase for safety, PK, with potential dose adjustment for each cohort

3 Sentinel subjects complete 8 days dosing in all cohorts. If stopping criteria are not met, remaining subjects in each cohort will be enrolled and randomized to treatment with BMN 111 or Placebo (1:1 ratio) and receive daily dosing for 52 weeks.

After the sentinel subjects reach 12 weeks of treatment, a DMC review will occur to evaluate all available safety and PK data.

DMC reviews safety and available PK data for the 3 sentinels, prior to enrollment in the next cohort. Upon approval by the DMC, the next younger cohort will be opened and the three sentinel subjects will be enrolled

Table 9.1.1: Schedule of Events

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1[u]	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (±7d)[y]	Early Term Visit
Informed consent	X													
Medical history[c]	X													
Parental height[d]	X													
Diagnostic genetic testing to confirm achondroplasia (if needed)[e]	X													
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[h]	X	X			X		X	X	X	X	X	X	X	X
Echocardiogram	X													
Anthropometric measurements[i]	X	X					X	X		X	X	X		X
Clinical laboratory assessments (hematology, chemistry, urinalysis)[j]	X				X	X	X		X		X	X		X
Thyroid function tests	X											X		
Vitamin D, 25-hydroxy test	X											X		
Salivary cortisol	X									X		X		X
Serum prolactin	X									X		X		X
Pharmacokinetics assessments[k]		X						X		X	X	X		
Anti-BMN 111 immunogenicity[l]		X						X		X		X		X
Genomic biomarkers (optional)							X					X		

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1[u]	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (±7d)[y]	Early Term Visit
Bone metabolism blood biomarkers[m]	X				X		X		X		X			X
Bone metabolism urine biomarkers[n]		X	X	X		X		X		X		X		X
BMN 111 pharmacodynamic urine biomarkers[n]		X	X	X		X		X		X		X		X
Urine chemistry[n]		X	X	X		X		X		X		X		X
Screening baseline hip assessment	X													
Hip monitoring[o]										X		X		X
MRI brain/skull[p]	X											X		X
Sleep study[q]	X									X		X		X
Clinical outcome assessment: Bayley-III	X									X		X		X
Clinical outcome assessment: WeeFIM[r]	X									X		X		X
Clinical outcome assessment: ITQOL	X									X		X		X
Clinical outcome assessment: CBCL[r]	X									X		X		X
DXA (BMD and BMC of whole body [less head], including spine, one third forearm and tibia, ultra distal radius	X											X		X
AP and lateral X-rays of spine[s]	X											X		X

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1[u]	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (±7d)[y]	Early Term Visit
AP X-rays of lower extremities[s]	X											X		X
Clinical photographs (optional)[t]	X											X		X
Capture achondroplasia-related procedures		X	X	X	X	X	X	X	X	X	X	X	X	X
BMN 111 or placebo administration[u]		All visits												
BMN 111 or placebo accountability		All visits												X
Adverse events[v]		All visits											X	X
Concomitant medications[w]	X	All visits											X	X
Phone call or home health visit[x]		Weekly calls for 6 months and then every 2 weeks for the remainder of the study												

[a] Clinic visits (except Days 1, 2, 3, and 8) have a ± 7-day window. Anthropometric measurement and imaging assessments can be conducted either pre-dose or post-dose.

[b] All blood tests at Screening visit should be obtained between Day -30 and Day -14.

[c] 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.

[d] 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, the parent can provide their stated height instead if consent has been given.

[e] If subjects had previous genetic testing, subjects must have a lab certification documenting the specific mutation required for the 111-206 study, including the identification of FGFR3 mutation (G346E, G375C, G380R, or "other").

[f] Complete physical exam includes 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.

[g] 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, BP, and respiratory rate.

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

1. Vital sign measurements are taken once per time point, preferably in a sitting position, after at least 5 minutes of rest.
2. Heart rate, blood pressure, and respiratory rate should be taken and recorded at each indicated time point.
3. When blood samples and vital sign assessments are scheduled at the same time or within the same time window, vital signs should be measured before blood samples are drawn.
4. If a vital sign measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and wait several minutes before measuring vital signs.
5. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
6. If a subject has a hypotensive event, or signs potentially consistent with hypotension, or a decrease of 20 mm Hg systolic BP or more from baseline (defined by pre-dose vitals collected that day), vital signs should be measured and recorded approximately every 15 minutes (± 5 minutes) for the first hour and every 30 minutes (± 5 minutes) thereafter until the BP returns to baseline (or within the normal range for this subject as defined by PI) and signs (if present) resolve.
7. If the decision is made to adjust the dose, vital signs will be obtained for at least 4 hr following the first dose at the adjusted dose level, similar to the Day 3, 8 schedule.

[h] A standard 12-lead ECG will include heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. The time of collection will be recorded. ECGs should be performed in triplicate with the subject supine at the visits indicated in the Schedule of Events. For study day visits in which study drug is given, ECGs will be performed post-dose. For Day 1, in addition to post-dose, ECGs will be performed pre-dose.

[i] Growth measures may be collected in triplicate 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 length, standing height (if able to stand unsupported), crown-to-rump length, head circumference, upper and lower arm and leg, and arm span. Measurements not taken in the midsagittal plane should be taken on the right side of the body if possible and should always be taken on the same side of the body throughout the study.

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

[k] PK plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes.

[l] Antibodies: Total anti-BMN 111 (TAb) and neutralizing antibody (NAb) samples (serum) will be drawn pre-dose at each time point listed on the SOE. NAb testing will be performed only on TAb positive samples from subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg. Drug-specific IgE will be drawn

pre-dose on Day 1 for subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg to stay within the limits of permitted blood volume collections in infants. Total immunoglobulin E (IgE) and drug-specific IgE will be drawn in the event of Grade 3 hypersensitivity adverse event) or at Investigator or Sponsor discretion. If such an event occurs, the drug-specific IgE sample should be drawn at least 8 hours after the event start time or 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 an unscheduled safety visit.

[m] Bone metabolism blood biomarkers will be waived at screening for subjects weighing < 7.0 kg to limit the blood volume on the smallest subjects at this visit. Serum samples for bone metabolism biomarkers will be collected pre-dose on the indicated visits.

[n] Urine biomarkers and urine chemistry (urine creatinine test) should be obtained pre- and post-dose (approximately 2-4 hours after study drug administration) for subjects when possible at the indicated visits. The time of collection will be recorded.

[o] 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. Adverse changes from baseline will trigger further evaluation.

[p] Obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC).

[q] If sleep study is uninterpretable, subject may need to repeat assessment. Obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC).

[r] WeeFim is waived for children < 6 months old; CBCL is waived for children < 18 months old.

[s] AP lumbar, lateral lumbar, and AP lower extremities are obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC). AP lower extremities X-ray at the Week 52 visit is waived for subjects who cannot stand upright unsupported.

[t] To document the physical and phenotypic findings of achondroplasia with and without treatment with study drug, clinical photography of the full body, face, spine, and extremities will be conducted. This assessment is optional. If the parents/caregivers decline clinical photography, the assessment will be waived for the duration of the study.

[u] All subjects should be injected in the left upper thigh on Day 1 unless clinically contraindicated. Thereafter, injection site should be rotated as described in the BMN-111 Injection Guide.

[v] 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.

[w] All medications (prescription, over-the-counter, herbal, topical) and nutritional supplements taken 30 days prior to screening and throughout the study should be documented.

[x] During the call study staff will ask the caregiver about correct administration procedures, record adverse events (AEs), record concomitant medications, and answer questions.

[y] The 4-week safety follow up visit will be waived for subjects who enter another BMN 111 study or registry within the 4-week period following last dose of study drug.

Table 9.1.2: Schedule of Events Observational Period for Cohort 3

Assessments	Screening[b]	Day 1[b] (Month 0)	3 Months (± 10 days)
Informed consent[a]	X		
Medical history, including growth history and ACH related history	X		
Concomitant medications	X	X	X
Physical examination[c]	X		
Vital signs[d]	X	X	X
Anthropometric measurements[e]		X	X
Vitamin D, 25-hydroxy[f]	X		X
Alkaline phosphatase[f]	X		X
Bone metabolism blood biomarkers	X		X
Bone metabolism urine biomarkers	X		X
Genomic biomarkers (optional)[g]		X	
Weight		X	X
Body mass index (calculated)		X	X
Clinical outcome assessment: Bayley-III[h]		X	
Clinical outcome assessment: ITQOL[h]		X	
Adverse events[i]	X	X	X

[a] Written informed consent and assent (as appropriate) will be obtained within 10 days before Study Day 1 (Month 0).

[b] Screening and Day 1 (Month 0) assessments may be performed on the same calendar day at the discretion of the investigator. If Screening and Day 1 (Month 0) are done on the same day, vital signs are taken only once. Please refer to eCRF Completion Instructions.

[c] A complete physical examination will be performed at Screening at the 3-month visit. Complete physical exam includes 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.

[d] Vital signs will be measured with appropriate blood pressure cuffs for achondroplasia children following detailed instructions in Study Reference Manual. At screening, blood pressure should be taken with subject in a sitting position, after the subject has been resting for at least 5 minutes, then the subject will

stand and BP will be taken again at approximately 1 and 3 minutes after standing. At all other visits, blood pressure should be taken one time after at least 5 minutes of rest, with subject in a sitting position. Heart rate should be taken at each time point that blood pressure is measured. Left brachial arm should be the first method of assessment considered, and the same site should be used for blood pressure measurement in each subject throughout the study. The method and site of blood pressure measurement will be recorded and should be utilized consistently throughout the remainder of the study.

[e] Growth parameters (anthropometric measurements) may include but are not limited to height, standing height, sitting height, weight, upper and lower arm and leg length, and arm span. Body proportion measurements may include but are not limited to upper:lower body segment ratio, upper arm:forearm length ratio, upper leg:lower leg length ratio, and arm span:standing height ratio. Refer to the Anthropometric Measurement Guidelines for specific instructions regarding the collection of growth measurements. All age-appropriate physical measurements will be collected at approximately the same time each visit (±2 hours) by a trained study staff member; every effort will be made to have the measurements collected by the same study staff member, if possible, throughout the study. Each measurement will be taken in triplicate (excluding weight, taken once).

[f] Vitamin D (25-hydroxy) and alkaline phosphatase will be measured during Screening and at the 3-month visit.

[g] If sample is not collected at Day 1, it may be drawn at any time during the study. The sample will be used for exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signaling.

[h] Bayley-III is waived for subjects < 1 month old; ITQOL is waived for subjects < 2 months old.

[i] AEs will be collected at screening after the ICF is signed.

9.1.1 Dose Adjustments

Analysis of available PK data from studies 111-101 and 111-202 indicated that differences in subject body weight did not directly translate to differences in total body clearance of BMN 111. The same weight-based dose in the pediatric population of Study 111-202 (5-12 years old) yielded lower exposure (C_{max} and AUC) than that characterized in the adult population of Study 111-101. Therefore, the same weight-based dose in the young pediatric population in this study may yield exposure less than the target exposure range characterized to be safe and effective in Study 111-202 at the 15-µg/kg dose. Since this is the first experience with BMN 111 in this young pediatric population, it is also possible the exposure at 15 µg/kg could be greater than the target exposure range, and dose adjustment may be warranted. Thus, an option for adjustment of the weight-based dose is provided to ensure that the appropriate target exposure for safety and efficacy is reached for the young subjects in this study.

The need for dose adjustment will be evaluated as follows: three sentinel subjects in Cohort 1 will receive an initial dose of 15 µg/kg. After all three sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety and PK data (at minimum). If the criteria for dose adjustment are met, the three sentinel subjects will be started on the new adjusted dose at their next scheduled visit, and vital signs will be obtained for at least 4 hours post-dose.

The remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. After the third sentinel subject reaches day 30 post dose adjustment, a DMC review will occur to evaluate all safety and PK data and, upon endorsement, the three sentinel subjects from the next younger cohort will be enrolled starting at the new adjusted dose. The three sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment.

Criteria for Dose Adjustment

The criteria for dose adjustment are based on obtaining equivalent exposure characterized to be safe and effective with the 15-µg/kg dose in Study 111-202 in each of the age cohorts evaluated in this study. BMN 111 dose may be adjusted if the mean observed $AUC_{0\text{-}120}$ from sentinel subjects is less than the 25th percentile for $AUC_{0\text{-}120}$ in Cohort 3 (15 µg/kg) of Study 111-202 or greater than the 75th percentile in Cohort 3 of Study 111-202. If these criteria are met, an allometric scaling coefficient, α, for BMN 111 clearance by subject body weight will be determined using a population PK modelling approach and available data from this study

and Studies 111-202 and 111-101. The recommended adjusted dose will be determined using the following expression:

$$Dose_{ch} = Dose_{ref}\left(\frac{WT_{ch}}{WT_{ref}}\right)^{\alpha}$$

where WT_{ref} and $Dose_{ref}$ are the typical (i.e., median) subject body weight and total dose, respectively, at the 15 µg/kg dose level in Cohort 3 of Study 111-202, and WT_{ch} is the anticipated median weight in the age cohort being studied. As such, the recommended adjusted dose will target the median $AUC_{0\text{-}120}$ observed at the 15 µg/kg dose level of Study 111-202. The recommended adjusted dose, $Dose_{ch}$, will be normalized by WT_{ch}, to provide the recommended adjusted weight-based dose. The following rules will be used for dose adjustment:

- A maximum of a 2-fold increase in dose/kg will be permitted between dose adjustments regardless of exposure.
- The total dose will not exceed the highest total dose administered in Study 111-202.

9.1.2 Stopping Criteria

Individual Subject Stopping Criteria

For individual subjects treated with BMN 111, DMC will be informed if any of the following individual subject stopping criteria should occur. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the individual subject will be considered.

- Any treatment-emergent adverse event (AE) assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (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
- Clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec
- Clinically significant new or worsening signs of cervicomedullary compression as determined by the Investigator and in consultation with Sponsor medical monitor and neurosurgical specialist (if needed)

- Adverse findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as determined by the Investigator and in consultation with Sponsor Medical Monitor and orthopedic specialist (if needed)

If the subject meets any stopping criterion, 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
- Permanent treatment discontinuation (with an option of ongoing assessment in the study)

Cohort Stopping Criteria

For each cohort, a DMC review will be conducted if any of the following cohort stopping criteria occur in subjects treated with BMN 111. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the cohort(s) will be considered and the impact on all other age cohorts will be assessed.

- Any treatment-emergent AE assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have a treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any two subjects cohort have a Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Any two subjects have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec
- Any two subjects have adverse 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)

9.2 Discussion of Study Design, Including Choice of Control Group

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are age 0 to

< 60 months. Identification of efficacy at this age range is congruent with mechanism of action of BMN 111, because BMN 111 is expected to act at open epiphyseal growth plates. Therefore, to have a potential therapeutic benefit for subjects with ACH, treatment is expected to be required prior to epiphyseal growth plate closure.

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

9.3 Selection of Study Population

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

Additional criteria for participation in the study are provided in Sections 9.3.1 and 9.3.2.

9.3.1 Inclusion Criteria

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

1. Diagnosis of ACH, confirmed by genetic testing. If subjects had previous genetic testing, subjects must have a lab report from a certified laboratory with the study specific mutation documented.
2. Age 0 to < 60 months, at study entry (Day 1)
3. Cohort 1 and 2 subjects must have at least a 6-month period of pretreatment growth assessment in Study 111 901 immediately before study entry, and have one documented measurement of height/body length a minimum of 6 months (+/- 10 days) prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrollment in Study 111-901 or (2) via enrollment in this Study 111 206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment.
4. Parent(s) or guardian(s) (and the subjects themselves, if required by local regulations or ethics committee) 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
5. Willing and able to perform all study procedures as physically possible
6. Parent(s) or caregiver(s) are willing to administer daily injections to the subjects and complete the required training

9.3.2 Exclusion Criteria

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

1. Have hypochondroplasia or short-stature condition other than achondroplasia (e.g., trisomy 21, pseudoachondroplasia, etc.)
2. Subject weighs < 5.0 kg (Cohort 1 and 2) or < 4.0 kg (Cohort 3)
3. Have any of the following:
   - Hypothyroidism or hyperthyroidism
   - Insulin-requiring diabetes mellitus
   - Autoimmune inflammatory disease (including celiac disease, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, etc.)
   - Inflammatory bowel disease
   - Autonomic neuropathy
4. Have a history of any of the following:
   - Renal insufficiency defined as serum creatinine > 2 mg/dL
   - Chronic anemia or Hgb < 10.0 g/dL (based on screening clinical laboratory testing)
   - Baseline systolic blood pressure (BP) below age and gender specified normal range or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms e.g., dizziness, fainting) or recurrent symptomatic orthostatic hypotension
   - Cardiac or vascular disease, including the following
     - Cardiac dysfunction (abnormal echocardiogram determined to be clinically significant by PI and medical monitor) at Screening Visit
     - Hypertrophic cardiomyopathy
     - Pulmonary hypertension
     - Congenital heart disease with ongoing cardiac dysfunction
     - Cerebrovascular disease
     - Aortic insufficiency or other clinically significant valvular dysfunction
     - Clinically significant atrial or ventricular arrhythmias
5. Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening ECG
6. Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator based on the following assessments:
   - Physical exam (e.g., neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins)
   - Polysomnography (e.g., severe central sleep apnea)
   - MRI indicating presence of severe CMC or spinal cord damage

7. Have an unstable medical condition likely to require surgical intervention in the next 6 months, or planned spine or long-bone surgery (i.e., surgery involving significant disruption of bone cortex) during the study period
8. Have documented uncorrected Vitamin D deficiency: 25(OH)D $\leq$15 ng/mL (37.5 nmol/L)
9. Require any other investigational product prior to completion of the study period
10. Have received another investigational product or investigational medical device within 30 days prior to the Screening visit
11. Have used any other investigational product or investigational medical device for the treatment of achondroplasia or short stature at any time
12. Require current chronic therapy with antihypertensive medication or any medication that, in the investigator's judgment, may compromise the safety or ability of the subject to participate in this clinical study
13. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (>3 months) at any time
14. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the 12 months prior to screening
15. Have ever had spine or long-bone surgery (i.e., surgery involving disruption of bone cortex) or have ever had bone-related surgery with chronic complications
16. Have ever had limb-lengthening surgery or plan to have limb-lengthening surgery during the study period
17. Have had a fracture of the long bones or spine within 6 months prior to screening
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin greater than upper limit of normal (ULN) at screening (except for subjects with a known history of Gilberts or newborns entering screening in Cohort 3)
19. Have evidence of severe untreated sleep apnea; or have newly initiated sleep apnea treatment (eg, CPAP or sleep apnea-mitigating surgery) in the 2 months prior to screening
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 history of hip surgery or severe hip dysplasia
23. Have a history of clinically significant hip injury in the 30 days prior to screening
24. Have a history of slipped capital femoral epiphysis or avascular necrosis of the femoral head
25. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the Investigator
26. 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
27. Have any concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, for any reason

9.3.3 Removal of Subjects from Treatment or Assessment

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

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

1. Subject experiences a serious or intolerable AE due to BMN 111 as determined by the subject, investigator, or sponsor
2. Subject requires medication or medical procedure prohibited by the protocol
3. Subject does not adhere to study requirements specified in the protocol
4. Subject is lost to follow-up

If a subject fails to return for scheduled visits, a 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 contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as HIPAA in the US, from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

It is a priority of the study to maximize study subject retention and adherence to study-specific procedures. The completeness of the study data may affect the integrity and accuracy of the study results. Therefore, subjects who discontinue study treatment should be

encouraged to continue to undergo as many of the protocol-specified procedures and assessments as possible for the remainder of the study, as long as such continued participation does not detrimentally affect the health, safety, or welfare of the subject.

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

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

9.3.4 Subject Identification

Each subject will be assigned a unique subject identifier. This unique identifier will be on all eCRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

9.3.5 Duration of Subject Participation

Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in both treatments groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term. For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

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

Follow-up assessments and procedures should be performed as outlined in the Study 111-206 Schedule of Events (Table 9.1.1 and Table 9.1.2).

Subjects who discontinue from study treatment will be asked to complete study assessments and procedures for the remainder of the study. If subjects discontinue from study treatment and decline to participate for the remainder of the study, they will be asked to return for a final follow-up visit 2 weeks after their last study visit, and the agreement should be documented.

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

9.4 Treatments

9.4.1 Treatments Administered

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

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

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

9.4.1.1 Study Drug Administration

During the study, BMN 111 or placebo will be administered as a single 15 µg/kg SC injection given daily at approximately the same time each day whenever possible. The same injection site should not be used 2 days in a row, and should be rotated between the 4 injection sites (upper thigh, upper back of arm, abdomen or buttocks). Doses may be administered in any of the common SC areas (upper arm, thigh, abdomen, buttocks). Following administration of each dose, subjects will be observed for at least 2 hours after the injection for Days 1 to 3, and 30 minutes for all other days of dose administration (longer if clinically indicated) either in the clinic by study personnel, by a home health nurse, or by a parent/caregiver. Instructions for home administration of BMN 111 or placebo for subjects

who qualify for parent/caregiver administration are provided in the Study Drug Injection Guide and Injection media.

9.4.2 Identity of BMN 111

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

PGQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC

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

9.4.2.1 Product Characteristics and Labeling

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

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

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

9.4.3 Storage

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

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

9.4.4 Directions for Administration

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

The injection will be administered as a daily dose of BMN 111 15 µg/kg or placebo given as a single subcutaneous injection. The dose should be given at approximately the same time every day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic. Subjects should have adequate food intake prior to dosing. In the hour prior to injection, all subjects should have been fed prior to administration of BMN 111 or placebo.

Caregivers will administer BMN 111 or placebo at home once approved by the investigator and adequate training is demonstrated. Instructions on how to complete and document the training can be found in the Study Reference Manual.

A caregiver will be eligible to administer BMN 111 or placebo if he or she meets all of the following criteria:

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

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

The caregiver will be provided with a study diary and will be asked to record daily dosing information, changes in health status, medications and injection sites used, date and time of the injection, and injection site reactions, if any.

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

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 ratio, i.e., injection with placebo:15 µg/kg of BMN 111, using IXRS. An independent third party vendor will develop the randomization schedule so that BioMarin and site personnel are blinded to treatment assignments.

9.4.6 Selection of Dose and Dosing Schedule Used in the Study

Study 111-202, the second clinical trial in humans and the first in children with ACH, is an ongoing Phase 2, open-label, sequential-cohort, dose-escalation study that assesses daily SC BMN 111 in pediatric subjects with ACH aged 5-14 years with doses ranging from 2.5 µg/kg to 30 µg/kg.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at the doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated. The most common AEs across all cohorts were injection site reactions, asymptomatic hypotension, headache, and nasopharyngitis. Based on previous experience of the ongoing Phase 2 clinical trial, including the 24-month data cut at 15 µg/kg, injection site reactions have been identified as risks associated with BMN 111 injections. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

Analysis of efficacy data from the 6-month initial phase of Study 111-202 showed that subjects treated with BMN 111 for 6 months at doses ranging from 2.5 to 15 µg/kg daily had a dose-dependent improvement in AGV, with ~50% improvement in AGV seen at the 15 µg/kg dose. The data from Cohort 4 (30 µg/kg) show an apparent greater than dose-proportional increase in BMN 111 plasma exposure (C_{max} and AUC_{0-t}), 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).

Efficacy/toxicity studies have been conducted in neonatal and very young animals (7-day postpartum mouse and rat) in both a disease (TD mouse) and non-disease (rat) model.

Given that this is the first study in infants and young children, an age-based cohort study design is used to assess safety and PK in young children (Cohort 1, ≥ 24 to < 60 months) prior to dosing toddlers (Cohort 2, ≥ 6 to < 24 months) and infants (Cohort 3, 0 to < 6 months). PK will be monitored and evaluated; Day 1 PK data from the sentinel subjects will inform dose selection modification for the sentinel subjects and for the rest of the cohort to target the observed exposure of the 15-µg/kg dose group in Study 111-202. Safety, efficacy and PK data from Study 111-202, a Phase 2 study in children with ACH, where a dose of 15 µg/kg has been and continues to be studied, are expected to be the most relevant, and translatable to this study (111-206).

9.4.6.1 Selection of Timing of Dose for Each Subject

9.4.7 Blinding

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

The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure. In the event of an emergency medical situation where subject management would be determined or significantly altered by knowing the treatment assignment, the investigator may be unblinded without prior written approval from the Medical Monitor. Following such an emergency unblinding, the investigator will contact the medical monitor and provide written rationale according to the unscheduled unblinding procedure set forth in the Study Manual. The Medical Monitor will review the rationale, evaluate whether there are any additional safety considerations that need to be implemented for the subject and/or the study, and determine whether the investigator requires further guidance on unblinding. The Medical Monitor may also communicate with the investigator advice on the care of the subject and define the plan for the subject's future participation in the study.

9.4.8 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 eCRF. The Investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any contraindicated medications immediately

thereafter. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

9.4.9 Treatment Compliance

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

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

9.5 Investigational Product Accountability (BMN 111 or Placebo)

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

9.5.1 Return and Disposition of Clinical Supplies

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

Unused BMN 111 or placebo may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for destruction. The study monitor must account for all BMN 111 or placebo kits/vials in a formal reconciliation process prior to destruction. The site must document all BMN 111 or placebo destroyed on site, and documentation must be provided to BioMarin and retained in the investigator study files. If a site is unable to destroy BMN 111 or placebo appropriately, the site can, upon request, return unused BMN 111 or placebo to the BioMarin contracted facility. The return of all BMN 111 or placebo kits/vials must also be documented and accounted for per instructions provided by BioMarin.

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

9.6 Dietary or Other Protocol Restrictions

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

Subjects should have an adequate food intake. In the hour prior to injection, all subjects should be fed prior to administration of BMN 111 or placebo.

9.7 Demographic Data and Medical History

Demographic data and a detailed medical history will be obtained at Screening. This 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; and evaluation for knee, thigh, hip or groin pain, or change in gait/activity.

9.8 Biological Parental Standing Height

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

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. Other body systems may be examined. Screening results will be the baseline values and clinically significant changes from baseline will be recorded as an AE or SAE and study drug related or unrelated when appropriate based on the investigator's clinical judgment.

9.10 Echocardiogram

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

9.11 Efficacy and Safety Variables

9.11.1 Efficacy and Safety Measurements Assessed

The Schedule of Events (Table 9.1.1 and Table 9.1.2) describes the timing of required evaluations.

9.11.2 Primary Efficacy Variables

The primary efficacy endpoint is change from baseline in length/height Z-score.

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

9.11.3 Secondary Efficacy Variables

The secondary efficacy endpoints include change from baseline in AGV (annualized to cm/yr), biomarker samples to evaluate the effect of BMN 111 on bone metabolism, and BMN 111 pharmacodynamic biomarkers.

Weight will be measured at Screening and at study visits as indicated on the Schedule of Events (Table 9.1.1 and Table 9.1.2).

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

Samples for blood and/or urine biomarkers will be collected at the time points presented in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Refer to the Study Laboratory Manual for instructions regarding obtaining and shipping samples. The sample type will also be included in the Study Laboratory Manual.

9.11.4 Exploratory Efficacy Variables

9.11.4.1 Body Proportion Ratios of the Extremities

Change from baseline in body proportion ratios of the extremities will be evaluated using anthropometric measurements and measurement ratios. Refer to the Anthropometric Measurement Guidelines for specific instructions regarding the collection of growth measurements. All age-appropriate physical measurements will be collected at approximately the same time each visit (±2 hours around the time when the first measurement assessment was taken at Screening) by a trained study staff member; every effort will be made to have the measurements collected by the same study staff member, if possible, throughout the study. Each measurement will be taken in triplicate (excluding weight, taken once).

Anthropometric measurement can be conducted either pre-dose or post-dose. Measurements may include but are not limited to length, standing height (if able to stand unsupported), crown-to-rump length, head circumference, upper and lower arm and leg, and arm span. Measurements not taken in the midsagittal plane should be taken on the right side of the body if possible and should always be taken on the same side of the body throughout the study

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

9.11.4.2 Imaging Assessment Procedures (per Schedule of Events)

Imaging assessment procedures for all visits must be performed using the same instruments. Imaging assessments can be conducted either pre-dose or post-dose.

- Bilateral lower extremity x-rays including both anterior-posterior (AP) and lateral views to assess growth plates.
- Hip imaging via pelvis x-ray to identify hip pathology (if changes from baseline trigger further evaluation)
- Lumbar spine x-rays to measure changes from baseline in bone morphology and pathology.
- MRI to evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions.
- DXA scan (whole body [less head], including spine, one third forearm and tibia, ultra distal radius) to assess bone mineral density (BMD) and bone mineral content (BMC).

Additional imaging may be conducted should there be any issues or concerns with the subject's imaging assessments. Imaging assessments will be collected and interpreted by a

central reader. If clinically significant abnormalities are noted, the investigator or designee is required to assess whether it is appropriate to report an AE and if the subject should continue in the study. Refer to the vendor Imaging Guidelines for detailed imaging assessment requirements and procedures.

9.11.4.3 Exploratory Biomarker Research Sample Analyses

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

For each portion of the blood and urine samples reserved for protocol-specified analyses, there may be multiple sample aliquots. Once samples have been successfully analyzed during the study, unused sample portions may be used during the study for assay development or other purposes stated in this section. No exploratory genomic research will be conducted without consent from the subject and his/her legally authorized representative (parent or legal guardian).

9.11.4.4 Genomic Biomarker Analysis

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

9.11.4.5 Sleep Study

Given that sleep apnea is a finding in children with ACH (Waters, 1993) and has implications on functional and health outcomes, a sleep study will be performed in a limited number of qualified sleep centers. A sleep-testing device will be used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea will include, but may not be limited to, the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index).

9.11.4.6 Clinical Photography

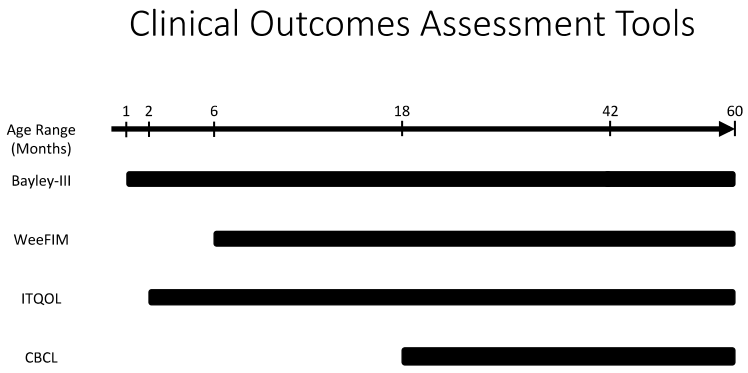
To document the physical and phenotypic findings of achondroplasia with and without treatment with study drug, clinical photography of the full body, face, spine, and extremities

will be conducted. This assessment is optional. If the parents/caregivers decline clinical photography, the assessment will be waived for the duration of the study.

9.11.4.7 Clinical Outcome Assessments

Clinical outcome assessments will be administered to assess the health-related quality of life of study subjects. ADL questionnaires will be performed in study subjects to assess functional performance. Clinical outcome assessments will be performed at the time points indicated in the Schedules of Events (Table 9.1.1 and Table 9.1.2). The age ranges for clinical outcome assessment tools are shown in Figure 9.11.4.7.1.

Figure 9.11.4.7.1: Clinical Outcomes Assessment Tools



9.11.4.7.1 Bayley-III

The Bayley-III is a performance based outcome assessment for use in children from 1 to 42 months. It is individually administered by the trained clinician to the subject/child. The time required varies from 15-60 minutes depending on the child's developmental level and cooperation.

Scales include Cognitive subscale, Receptive and Expressive subscales, and Gross and Fine Motor subscales. The two language scales make up a composite Language Scale score and the Gross and Fine Motor subscales yield a composite Motor Scale score. In addition, there is a Social-Emotional Scale and Adaptive Behavior Scale, which is a questionnaire read and completed by parent or caregiver.

The scales have clinical and research utility as a diagnostic assessment for young children with varied disorders and disabilities, and reflect current professional standards for early childhood assessment (Bayley, 2006).

In addition to its use for subjects ranging from 1 to 42 months old, the Bayley-III assessment will be administered to those between 42 and 60 months old (Figure 9.11.4.7.1), as this assessment can capture ongoing developmental issues associated with Achondroplasia. Bayley-III is waived for subjects < 1 month old.

9.11.4.7.2 Activity of Daily Living and Functional Independence Measure (Wee-FIM)

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

The Wee-FIM instrument has been used in previous research in children with ACH, and has identified ongoing limitations in functional performance across these domains extending beyond the age of 7 years (Ireland, 2011). Because the WeeFIM considers the child's performance from a caregiver's perspective (Ireland, 2012), this tool in turn gives an indication of "burden of care" for families and caregivers of children with ACH. WeeFim is waived for children < 6 months old.

9.11.4.7.3 ITQOL

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

9.11.4.7.4 Child Behavior Checklist

The Child Behavior Checklist (CBCL) is for use in children from 1.5-5 years old. The CBCL comprises 99 questions addressing symptoms related to mood, behavior issues, and sleep disturbance. It is completed by the parent or primary caregiver.

The form requires approximately 15 minutes to complete. The checklist yields scores in the following areas: reactivity, anxiety, depression, somatic complaints, withdrawal, sleep problems, attention problems, and aggressive behavior. CBCL is waived for children < 18 months old.

9.11.5 Pharmacokinetics Variables

PK plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes.

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

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

9.11.6 Safety Variables

Safety will be evaluated by the incidence of AEs, SAEs, and clinically significant changes in vital signs, physical examination, ECG, imaging, and laboratory test results (urinalysis, chemistry, hematology). Additionally, imaging, hip monitoring, biomarker, immunogenicity, cortisol and prolactin levels, and physical measurement data will be utilized for safety-related reviews and analysis.

9.11.6.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject receives study drug. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10.2.1. Assessments of AEs will occur at the time points shown in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Additionally, contact by a study staff member to the caregiver will be required every week for 6 months, and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. Information

on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

9.11.6.2 Procedures due to Achondroplasia

All procedures/intervention/surgery due to underlying ACH will be recorded after informed consent is obtained and after the first administration of study drug, until 2 weeks after either the last administration of study drug or the Early Termination visit. If a subject is discontinued from the study prematurely, all procedures/intervention/surgery due to underlying ACH will be recorded at the Early Termination visit.

9.11.6.3 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1 and Table 9.1.2. The scheduled clinical laboratory tests are listed in Table 9.11.6.3.1. Refer to the Study Reference 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.

The investigator should assess all abnormal clinical results and include a comment on whether or not the result is clinically significant. Each clinically significant laboratory result should be recorded as an adverse event.

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 eCRF.

Table 9.11.6.3.1: 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
Glucose		

Blood Chemistry	Hematology	Urinalysis
Bicarbonate LDH Phosphorus Total protein 25-hydroxy Vitamin D Creatinine Thyroid function (TSH, FT4; if either TSH and FT4 are abnormal then T3 may be measured in addition)		Urine Chemistry Urine creatinine Urine sodium Urine potassium

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

9.11.6.4 Other Laboratory Assessments

Subjects will be asked to provide blood and urine at the times indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Blood volume for testing has been reduced to the minimum necessary for adequate evaluation of efficacy and safety of BMN 111.

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

Salivary cortisol and serum prolactin will be collected at the times indicated in the Schedule of Events (Table 9.1.1).

Scheduled biomarker and anti-BMN 111 antibody tests are listed in Table 9.11.6.4.1.

Table 9.11.6.4.1: Biomarkers and Anti-BMN 111 Antibodies

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

cGMP, cyclic guanosine monophosphate

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

Vital signs assessed pre-dose will include seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). All treatment visits have pre-dose vital sign assessments. Post-dose measurements include heart rate and BP. For all dosing visits, assessment frequency is detailed in Table 9.11.6.5.1 (Schedule of Events, Table 9.1.1 and Table 9.1.2).

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. Left brachial arm should be the first method of assessment considered, and the same site should be used for blood pressure measurement in each subject throughout the study. The method and site of blood pressure measurement will be recorded and should be utilized consistently throughout the remainder of the study.

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

If a subject has signs 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 signs (if present) resolve. If the hypotension resolves within the first hour and returns to the normal range, additional BP monitoring as described above is not required. Detailed guidance for blood pressure measurements is provided in the Blood Pressure Instrument and Technique Guidelines.

Table 9.11.6.5.1: Vital Sign Assessment Frequency

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

9.11.6.6 Mitigating the Risk of Potential Hypotension

Study personnel and caregivers should be made aware of the potential risk of hypotension with BMN 111 administration. Subjects must be well hydrated and at a minimum be fed prior to administration of BMN 111 or placebo. If a recent acute illness associated with volume depletion (e.g., nausea, vomiting, diarrhea) has not completely resolved prior to the first dose of BMN 111 or placebo, BMN 111 or placebo dosing may be delayed until hydration status has improved (up to the maximum period allowed for the screening window).

Caregivers should be trained to observe and recognize the signs of dehydration (e.g. from fever, vomiting, diarrhea, etc.) and contact the investigator prior to BMN 111 or placebo administration if dehydration is suspected. Site personnel and caregivers should be trained to identify the signs 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 10.3.1.4.

9.11.6.7 Electrocardiography

A standard 12-lead ECG will include heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. The time of collection will be recorded. ECGs should be performed in triplicate with the subject supine at the visits indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). For study day visits in which study drug is given, ECGs will be performed post-dose. For Day 1, in addition to post-dose, ECGs will be performed pre-dose. 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.

9.11.6.8 Hip Clinical Assessment

The hip clinical assessment should be completed by an appropriately qualified physical therapist or a physician (MD) i.e., the investigator or the sub-investigator at the time points indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Medical history will be obtained to evaluate for hip, thigh, or knee pain, or change in gait. The physical exam (including observation of gait when possible) identifies and evaluates any changes in hip function or pain with assessment of active and passive range of motion. Changes from baseline may trigger further evaluation based on the investigator's clinical assessment, which may include hip imaging and/or orthopedic consultation. If findings on clinical hip exam are determined to be clinically significant by the investigator and in consultation with Sponsor's Medical Monitor and orthopedic specialist (if needed), the DMC will be notified of AEs resulting from clinically significant abnormal hip monitoring assessments. DMC may provide recommendations as to if/when BMN 111 or placebo treatment should be temporarily or permanently discontinued.

9.11.6.9 Pediatric Blood Volume

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

To minimize blood collection volumes, assay technologies were chosen that are capable of sensitively detecting analytes using the lowest possible volume of blood for analysis. Additionally, assays capable of detecting analytes in urine rather than blood have been selected where possible.

9.11.6.10 Anti- BMN 111 Immunogenicity Assessments and IgE Testing

Subjects randomized to receive BMN 111 or placebo will undergo immunogenicity testing. Blood (serum) samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 9.1.1), and testing performed using validated assays. Neutralizing antibody (NAb) testing will be performed on Baseline and TAb positive samples drawn from subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg.

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

- Anti- BMN 111 total antibody (TAb)
- Anti-BMN 111 antibody cross-reactive with endogenous CNP, ANP, and BNP (TAb)
- Anti- BMN 111 NAb

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

9.11.6.11 HPA Axis Assessments

To address potential effects of BMN 111 on activation of the hypothalamic pituitary adrenal (HPA) axis, assessment of salivary cortisol and serum Prolactin levels will be analyzed at the time points indicated in the Schedule of Events (Table 9.1.1). Both tests will be done at Baseline, Week 26, and Week 52.

9.11.6.12 Ad Hoc Safety Assessments

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

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

- Drug-specific IgE
- Total IgE

- Serum tryptase

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

A localized injection site reaction is defined as skin signs or signs 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).

9.11.6.13 Unscheduled Safety Visits

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

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

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

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

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 1 or more of the following criteria:

- Is fatal
- Is life threatening

  Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs inpatient hospitalization. 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 subject exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction – that, based on medical judgment, may jeopardize the subject or require intervention to prevent one of the above consequences (e.g. anaphylaxis)

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

10.1.3 Events of Special Interest (EOSI)

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

- Fracture
- Slipped Capital Femoral Epiphysis (SCFE)
- Avascular necrosis or Osteonecrosis

10.2 Methods and Timing for Capturing and Assessing Safety Parameters

10.2.1 Adverse Event Reporting Period

For subjects enrolled in Cohort 1 (≥ 24 to < 60 months old) and Cohort 2 (≥ 6 to < 24 months old), the study AE reporting period is as follows: after informed consent but prior to initiation of study treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, all non-serious AEs and SAEs reporting period begins and continues until 4 weeks following either the last administration of study drug or the early termination visit, whichever is longer (refer to Section 12.1.11). The criteria for determining, and the reporting of, SAEs is provided in Section 10.1.2. For subjects enrolled in Cohort 3 (0 to < 6 months old), AE collection period begins after screening.

10.2.2 Eliciting Adverse Events

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

10.2.3 Assessment of Seriousness, Severity, and Causality

The Investigator or qualified designee responsible for the care of the subject 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 (e.g., MD/DO, physician's assistant, nurse practitioner, or DDS).

10.2.3.1 Seriousness

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

10.2.3.2 Severity

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

The Investigator or qualified designee will determine the severity of each AE and SAE, and EOSI 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 activities of daily living (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 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 eCRF. 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[a]	Description
Not Related	• Exposure to the IP has not occurred OR • The administration of the IP and the occurrence of the AE are not reasonably related in time OR • The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IP.
Related	• The administration of the IP and the occurrence of the AE are reasonably related in time AND • The AE could possibly be explained by factors or causes other than exposure to the IP **OR** • The administration of IP and the occurrence of the AE are reasonably related in time AND • The AE is more likely explained by exposure to the IP than by other factors or causes.

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

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

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

10.3 Procedures for Recording Adverse Events

10.3.1 Recording Adverse Events on a 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 (e.g., 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 sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, then this diagnosis should be entered on the AE form, replacing the original entries where appropriate.

10.3.1.2 Adverse Events Occurring Secondary to Other Events

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

10.3.1.3 Persistent or Recurrent Adverse Events

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

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

10.3.1.4 Hypotension

If an asymptomatic drop in blood pressure meets the protocol definition of AE per clinical judgment of the reporter, report the event as “blood pressure decreased.” If the drop in blood pressure is associated with signs or symptoms, complete the symptomatic hypotension eCRF and use the following guidance to report the corresponding AE eCRF: If a unifying diagnosis

is available to explain the event of hypotension, report the diagnosis as an AE and capture signs and symptoms on the symptomatic hypotension eCRF page. If no other unifying diagnosis is available, report "hypotension" as the event and capture signs and symptoms on the symptomatic hypotension eCRF page.

10.3.1.5 Injection Site Reactions

If an injection site reaction is associated with a single sign or symptom, report the event on AE eCRF page (e.g., redness at injection site, AE is injection site redness). If the injection site reaction is associated with multiple signs or symptoms, report injection site reaction as the adverse event on the AE page, and individual signs and symptoms will be reported on the ISR eCRF page (e.g., if the subject experiences redness and induration, report "Injection site reaction" on the AE page, and in the corresponding Injection eCRF page, report erythema and induration). If the injection site reaction appears after 24 hours, add "delayed" to the term used to describe the event.

10.3.1.6 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 it is not otherwise refuted by a repeat test to confirm the abnormality and **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 abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., 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.

10.3.1.7 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., *more frequent* headaches).

10.3.1.8 General Physical Examination Findings

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

10.3.1.9 Hospitalization, Prolonged Hospitalization, or Surgery

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

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

- Perform a protocol-mandated 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

10.3.1.10 Deaths

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

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

10.4 Reporting Requirements

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

10.4.1 Expedited Reporting Requirements

All SAEs and EOSI, if applicable 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 entering the information in the AE eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. Each SAE must also be reported on the appropriate eCRF. Investigators should not wait to collect information that fully documents the event before notifying BPV of an SAE. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit any information requested by BioMarin as soon as it becomes available.

If the electronic data capture (EDC) is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

The reporting period for SAEs begins after informed consent is obtained and continues until 4 weeks following either the last administration of study drug or study discontinuation/termination, 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 Subjects after Adverse Events

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

For some SAEs, the Sponsor may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (eg, hospital discharge summary, consultant report, 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 subject to report, to the Investigator and/or to BPV directly, any subsequent SAEs that the subject's personal physician(s) believes might be related to prior study treatment.

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

10.7 Urgent Safety Measures

The regulations governing clinical trials state that the sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, 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 subjects, the sponsor and the Investigator shall take appropriate urgent safety measures to

protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/EC/REB is notified at the same time."

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

The reporting period for these events which may require the implementation of urgent safety measures is the period from the time of signing of the ICF through the completion of the last study visit or at the Early Termination Visit (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
Phone: PI
Fax: PI
E-mail: drugsafety@bmrn.com

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

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

11 APPROPRIATENESS OF MEASUREMENTS

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

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

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

Bone-related biomarkers and other biochemical markers of the pharmacological activity of BMN 111 in the blood or urine are secondary assessments. Genomic biomarkers are exploratory assessments.

12 STUDY PROCEDURES

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

12.1 Treatment Visit(s)

12.1.1 Screening/Baseline Day -30 to Day -1

- Medical history
- Parental height
- Diagnostic genetic testing to confirm achondroplasia (if needed)
- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Echocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Thyroid function tests
- Vitamin D, 25-hydroxy test
- Salivary cortisol
- Serum prolactin
- Bone metabolism blood biomarkers
- Screening baseline hip assessment
- MRI brain/skull
- Sleep study
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- DXA

- AP and lateral X-rays of spine
- AP X-rays of lower extremities
- Clinical photographs (optional)
- Concomitant medications

12.1.2 Day 1 and Week 13 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Pharmacokinetics assessments
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Collection of ACH-related symptoms, tests, and interventions
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.3 Days 2 and 3

- Physical examination
- Weight
- Vital signs
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Collection of ACH-related symptoms, tests, and interventions

- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.4 Day 8 (±1d) and Week 20 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Bone metabolism blood biomarkers
- Collection of ACH-related symptoms, tests, and interventions
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.5 Week 3 (±7d)

- Physical examination
- Weight
- Vital signs
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Collection of ACH-related symptoms, tests, and interventions
- BMN 111 or placebo administration
- BMN 111 or placebo accountability

- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.6 Week 6 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Genomic biomarkers (optional)
- Bone metabolism blood biomarkers
- Collection of ACH-related symptoms, tests, and interventions
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.7 Week 26 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Salivary cortisol
- Serum prolactin
- Pharmacokinetics assessments
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers

- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Hip monitoring
- Sleep study
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- Collection of ACH-related symptoms, tests, and interventions
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.8 Week 39 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Pharmacokinetics assessments
- Bone metabolism blood biomarkers
- Collection of ACH-related symptoms, tests, and interventions
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.9 Week 52 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Thyroid function tests
- Vitamin D, 25-hydroxy test
- Salivary cortisol
- Serum prolactin
- Pharmacokinetics assessments
- Anti-BMN 111 immunogenicity
- Genomic biomarkers (optional)
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Hip monitoring
- MRI brain/skull
- Sleep study
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- DXA
- AP and lateral X-rays of spine
- AP X-rays of lower extremities
- Clinical photographs (optional)
- Collection of ACH-related symptoms, tests, and interventions

- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.10 Week 56 Safety Follow-up (±7d)

- Physical examination
- Vital signs
- Electrocardiogram
- Collection of ACH-related symptoms, tests, and interventions
- Adverse events
- Concomitant medications

12.1.11 Early Termination Visit

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Salivary cortisol
- Serum prolactin
- Anti-BMN 111 immunogenicity
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Hip monitoring
- MRI brain/skull (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)

- Sleep study (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- DXA
- AP and lateral X-rays of spine (obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination)
- AP X-rays of lower extremities (obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination)
- Clinical photographs (optional)
- Collection of ACH-related symptoms, tests, and interventions
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications

12.2 Observational Period for Cohort 3 (Infants between birth and <3 months old [0 days to <13 weeks])

12.2.1 Screening Visit

- Medical history, including growth history and ACH-related history
- Concomitant medications
- Physical examination
- Vital signs
- Vitamin D, 25-hydroxy
- Alkaline phosphatase
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- Adverse events

12.2.2 Day 1 (Month 0)

- Concomitant medications

- Vital signs
- Anthropometric measurements
- Genomic biomarkers (optional)
- Weight
- Body mass index (calculated)
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: ITQOL
- Adverse events

12.2.3 3 Months (± 10 days)

- Concomitant medications
- Vital signs
- Anthropometric measurements
- Vitamin D, 25-hydroxy
- Alkaline phosphatase
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- Weight
- Body mass index (calculated)
- Adverse events

13 DATA QUALITY ASSURANCE

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

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

Sites will enter study data into eCRFs into the study EDC system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS v. 9.4.

14.1.1 Interim Analyses

An interim analysis will be carried out to support NDA/MAA filing. The report will be provided by a third party to assure that the study team, subjects, and investigators have no access to the individual subject treatment allocation.

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

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

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

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

14.2 Safety Analysis

The safety analysis will be performed on safety population as defined in Section 14.7.2 and will be considered descriptive.

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

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment (as assessed by investigator), and severity. All AEs, including SAEs and AEs that lead to permanent discontinuation from the study and from the study treatment, will be listed. Hypersensitivity reactions and

symptomatic hypotension are of interest, and the percentage of subjects who report these AEs will be presented. Hypersensitivity reactions will be defined in the SAP.

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

All other safety measures including laboratory tests, vital signs, ECG, echocardiogram, hip clinical assessment, and concomitant medication data will also be summarized descriptively. Data summaries will be presented by treatment group (when applicable) for each cohort and overall. All safety results will be listed.

14.3 Efficacy Analysis

Efficacy analysis will be performed on the efficacy population as defined in Section 14.7.1. Efficacy endpoints include length/height AGV and length/height standard score (Z-score) at Week 52.

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

$$\text{AGV} = \frac{\text{Length/standing height at Day 2} - \text{Length/standing height at Day 1}}{\text{Interval Length (Days)}} \times 365.25$$

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

- Baseline: [Date of last length/height measurement in study 901 at least 6 months prior to screening visit in study 206, Date of Day 1]
- Week 13: [Date of Day 1, Date of Week 13]
- Week 26: [Date of Day 1, Date of Week 26]
- Week 39: [Date of Day 1, Date of Week 39]
- Week 52 (12-month): [Date of Day 1, Date of Week 52]

The baseline of the AGV is established in the natural history study of Study111-901, based on the standing height measurements in the last 6 months prior to enrollment to Study 111-206. AGV will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum). Results will be summarized by treatment group and cohort.

The measurement of length/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.

Comparisons between treatment groups by cohort on these variables will be carried out where appropriate. Statistical comparisons will be considered descriptive. Additional details regarding efficacy analysis will be provided in the SAP.

14.4 Pharmacokinetic Analyses

Subjects randomized to receive BMN 111 or placebo will undergo pharmacokinetic testing.

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

14.5 Immunogenicity Analysis

Immunogenicity will be summarized as change from baseline as well as by study time point in subjects randomized to receive BMN 111 or placebo. Results will be summarized as incidence and titer for all cohorts. Additionally, immunogenicity may be assessed for correlations with measures of safety, PK, and efficacy.

14.6 Determination of Sample Size

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

14.7 Analysis Populations

14.7.1 Efficacy Population

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

14.7.2 Safety Population

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

15 DATA MONITORING COMMITTEE

In addition to safety and PK 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. After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort will be opened and the 3 sentinel subjects will be enrolled.

The DMC will make recommendations for stopping or continuing the study on an individual subject level and/or on a cohort level per the pre-specified stopping criteria. Based on criteria outlined in the protocol, the DMC may also make endorsements for dose adjustments if needed.

Please see DMC Charter for further details.

16 COSTS, COMPENSATION, AND SUBJECT INJURY

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

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

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

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

eCRFs must be completed using a validated web-based application. Study site personnel will be trained on the application and will enter the clinical data from source documentation. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representative) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If direct source document verification of study data by the site monitor is prohibited by institutional policy or local law, then the Investigator must make available facilities and/or personnel to allow GCP-compliant source verification to occur. Examples of such methods include certified copies of records which have study data visible but sensitive information redacted, or other GCP-compliant means agreed between the Investigator and the Sponsor.

A CRA designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" (SDV). If an error is discovered at any time or a clarification is needed, the CRA, or designee, will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Before a subject's eCRF casebook can be locked, data fields must be source data verified and all queries closed. Refer to the 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 eCRFs 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 sent to each site for retention with other study documents.

18 STUDY MONITORING AND AUDITING

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

Members of BioMarin's GCP Compliance Department or designees may conduct an audit of a clinical site at any time before, during, or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an 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.

19 RETENTION OF RECORDS

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

20 USE OF INFORMATION AND PUBLICATION

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

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572 and/or principles of ICH E6 GCP, the Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes. He or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and/or ICH E6 Sections 2.9 and 4.8 are met, as well as IRB/IEC review and approval requirements in 21 CFR Part 56 and/or ICH E6 GCP Section 2.6.
- 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 and/or ICH E6 GCP Section 4.11.
- 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 are in accordance with 21 CFR 312.62 and/or ICH E6 Section 4.9, and will make those records available for inspection in accordance with 21 CFR 312.68 and/or ICH Section 4.9.7.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH Section 3.0 and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312 and/or ICH E6 R2.

23 SIGNATURE PAGE

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

Protocol Number: 111-206

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

Investigator Signature Date

Printed name: _____

Accepted for the Sponsor:

PI

PI

Date

Printed name: PI MD PhD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months
Protocol Number:	111-206
Active Investigational Product:	BMN 111 (modified rhCNP)
IND	111299
European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2016-003826-18
Indication:	Achondroplasia
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 2
Sponsor's Responsible Medical Monitor:	PI , MD, PhD PI BioMarin Pharmaceutical Inc. 10 Bloomsbury Way London WC1A 2SL
Study Design:	Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH
Treatment Duration	52 weeks
Duration of Subject Participation:	60 weeks for Cohorts 1 and 2 (screening, treatment, follow-up). Subjects in Cohort 3 who enter the study for a 12-week observational period will participate for approximately 70 weeks (screening, observational period, treatment, follow-up)
Dose:	15 µg/kg BMN 111 or placebo daily, subject to adjustment per protocol
Study Population:	Children 0 to < 60 months old with achondroplasia
Date of Original Protocol:	06 December 2017
Date of Amendment 1:	16 August 2018

1 RATIONALE AND SUMMARY OF CHANGES

The protocol has been amended to include the following changes:

1. The lower age range of participating subjects who have a ≥ 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry has been revised from ≥ 3 months to ≥ 6 months [§9.1].

   Rationale: To harmonize the roll-over of subjects from Study 111-901 to 111-206 in each cohort.

2. No two sentinel subjects will be dosed on the same day for any cohort [§9.1].

   Rationale: To enforce a minimum period of safety observation prior to dosing the next subject, as in each cohort, the sentinel subjects will be the youngest children to date dosed with BMN 111.

3. Echocardiogram will be performed at the Week 56 Safety Follow-up and Early Termination visits [Table 9.1.1; §12.1.10; §12.1.11].

   Rationale: To enable monitoring for any unintended adverse anatomical or functional cardiac adverse effects at the time of study completion.

4. Use of residual plasma samples for cGMP PD biomarker assessment in all age groups has been added to procedures [Table 9.1.1; Table 9.11.6.4.1; §12.1.2; §12.1.7; §12.1.8; §12.1.9].

   Rationale: Use of the residual sample allows for PD assessments in infants without timed urine collection. The infant group assessments can then be compared to all age groups.

5. An anti-BMN 111 immunogenicity assessment has been added at Week 3 [Table 9.1.1; §12.1.5].

   Rationale: Week 3 immunogenicity assessment has been added to characterize early anti-BMN 111 immune responses in this age range of the achondroplasia subject population.

6. Bone metabolism urine biomarkers, BMN 111 pharmacodynamic urine biomarkers, and urine chemistry assessments have been added at Week 39 [Table 9.1.1; §12.1.8]

   Rationale: To obtain PD assessments at each visit that PK is collected and to obtain creatinine concentrations for cGMP calculations

7. The sleep study scheduled at the Week 26 visit has been removed [Table 9.1.1; §12.1.7].

   Rationale: To minimize study burden on the trial participants, families and caregivers, as only two polysomnography studies are required to meet the study objectives. One

assessment will be performed at baseline and one at Week 52 (or the Early Termination Visit, if the subject leaves the study early).

8. DXA scans will no longer include tibia scans [Table 9.1.1; §9.11.4.2].

   Rationale: The tibia scan was removed because DXA machines are unable to properly perform the scan.

9. If the 111-901 visit at which the subject enters Study 111-206 and the 111-206 Screening visit are on the same day, the procedures common to both visits will be performed one time only [Table 9.1.1 (footnote b)].

   Rationale: To ensure that duplicate study procedures, including blood draws, are not repeated unnecessarily in this infant and toddler population.

10. On days when PK samples are being drawn, ECG will be performed within a 5-minute window prior to the 30-minute PK assessment [Table 9.1.1 (footnote h); §9.11.6.7].

    Rationale: This timing allows for ECG assessment in relation to BMN 111 C_{max}.

11. Exclusion criterion #6 has been revised from "…as determined by the Investigator *based on* the following assessments…) to (…as determined by the Investigator *and informed by* the following assessments…). The determination about whether presence of cervicomedullary compression is likely to require surgical intervention will be informed by physical exam, polysomnography, and MRI [§9.3.2].

    Rationale: To clarify that this is a clinical decision to be informed by signs, symptoms, and investigations, and not based solely on abnormal finding in an MRI.

12. Exclusion criterion #15 has been revised to include cervicomedullary decompression surgery (Cohorts 2 and 3 only) [§9.3.2].

    Rationale: To clarify that children with prior cervicomedullary decompression surgery are not eligible for entry into the study in Cohort 2 or 3. This is to enable formal evaluation of a potential treatment effect on the foramen magnum using MRI in children at ages where the foramen magnum is still growing rapidly. As the synchondroses around the foramen magnum are already closing after the age of two years, subjects with prior cervicomedullary decompression surgery may be allowed into Cohort 1 only after discussion and agreement with the Medical Monitor.

13. Inclusion/exclusion criteria have been added for Cohort 3 subjects enrolling in the observational period [§9.3.3; §9.3.4].

    Rationale: These criteria are used in our observational study 111-901 and apply only to Cohort 3 subjects who enroll in the 111-206 observation period.

14. A table of restricted medications, including growth hormone, has been added [§9.3.5].

Rationale: To ensure that growth hormone is not used concomitantly.

15. In Section 9.11.4.4, Genomic Biomarker Analysis, the text "of plasma DNA" has been removed from "Exploratory genomic analysis of plasma DNA may inform understanding of the BMN 111 mechanism of action…" [§9.11.4.4].

    Rationale: Genomic analysis implies DNA/RNA analysis, and we are not obtaining DNA from plasma.

16. For subjects enrolled in Cohort 3 (0 to < 6 months old), the collection period for all AEs begins after informed consent is obtained [Table 9.1.2 footnote h; §10.2.1].

    Rationale: to collect and document all AEs so as to establish robust baseline natural history in these subjects prior to study drug administration.

17. Administrative updates have been made to improve consistency and clarity.

    a. Text has been changed to reflect the age of majority rather than age 18, as the age of majority varies between countries. Section 5.3, *Subject Information and Informed Consent*.

    b. Section 7.3, *Ongoing Clinical Studies*, has been updated to include a description of Study 111-302 (Section 7.3.5).

    c. In Section 8, *Study Objectives*, in the secondary objective addressing evaluation for hip, thigh, or knee pain, or change in gait *from medical history,* the phrase "…from medical history…" has been removed to clarify that hip assessments are performed at screening, and these measures serve as a baseline for future assessments.

    d. Error in Section 9.1, *Overall Study Design and Plan*, description of Cohort 3 has been corrected to state that at least *17* additional subjects will be randomized.

    e. Clarification about age-appropriate dose adjustment has been added to indicate that subjects will be administered the recommended dose appropriate to their current age. Section 9.1, *Overall Study Design and Plan*, and Section 9.1.1, *Dose Adjustments*.

    f. The time window for the Week 56 safety follow-up visit has been changed from ± to + 7 days to allow a full 4 weeks between the last dose of study drug and the safety follow-up visit. Table 9.1.1, Section 12.1.10, *Week 56 Safety Follow-up*.

    g. Clarified that the screening/baseline hip assessment includes a pelvis x-ray. Table 9.1.1, Section 12.1.1, *Screening/Baseline Day -30 to Day -1*.

    h. Because the definition of ACH-related events differed between sites, capture of ACH-related events has been changed to capture all procedures listed in the Schedule of Events to ensure all procedures are collected and analyzed. Tables 9.1.1 and 9.1.2; Section 9.11.6.2; Sections 12.1.2-12.1.11; Sections 12.2.2-12.2.3.

i. Vital signs instructions now include sitting or supine positions to account for subjects who are too young to sit. The duration of vital signs assessments in Section 9.11.6.5 and Table 9.11.6.5.1 has been extended to align with the assessments presented in the SOE. Additionally, if a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1,2 schedule. Table 9.1.1, Vital Sign Assessment Frequency table; Section 9.11.6.5, *Vital Signs*; Table 9.11.6.5.1.

j. In the event that a sentinel subject has an interrupted dose of study drug on Day 1, instructions have been included for a change in the PK collection schedule. Table 9.1.1 footnote L; Section 9.11.5, *Pharmacokinetics Variables*.

k. Footnote m in Table 9.1.1 has been updated to correspond to the information in Section 9.11.6.10, *Anti-BMN 111 Immunogenicity Assessments and IgE Testing*.

l. In Table 9.1.1, footnotes n and o, and Section 9.11.3, *Secondary Efficacy Variables*, text has been added to specify the biomarkers used to assess changes in bone and collagen metabolism.

m. In Table 9.1.1, footnote q, instruction has been included that efforts to obtain a satisfactory MRI image can be discontinued after 3 unsuccessful attempts.

n. In Table 9.1.1, footnote v now includes instructions for managing a dose interruption.

o. Section 9.1.1, *Dose Adjustments*, has been corrected to state that a DMC review will occur after the third sentinel subject reaches Week 12 post-dose adjustment.

p. In Section 9.3.8, *Duration of Subject Participation*, final follow-up visit for subjects who discontinue from the study has been changed from 2 weeks to 4 weeks after last dose to be consistent with the safety follow-up at 4 weeks in the Schedule of Events.

q. In Section 9.4.1, *Treatments Administered*, text has been added to reiterate that sentinel subjects will be treated with BMN 111, versus randomized subjects who will receive either BMN 111 or placebo. Additionally, the BMN 111 dose level is subject to potential per-protocol adjustment.

r. Directions for subject observation following BMN 111 administration at study visits has been revised in Section 9.4.1.1, *Study Drug Administration*, for consistency with Section 9.4.4, *Directions for Administration*.

s. Text in Section 9.4.1.1, *Study Drug Administration* now indicates that study drug injections will be administered at age-appropriate sites, determined at the discretion of the investigator.

t. Text has been revised to indicate that in the hour prior to injection, all subjects should be well hydrated and fed. Section 9.4.4, *Directions for Administration*; Section 9.6, *Dietary or Other Protocol Restrictions*.

u. In Section 9.4.5, *Method of Assigning Subjects to Treatment Groups*, a note has been added that in Japan, subjects are randomized separately within each cohort.

v. Section 9.11.4.2, *Imaging Assessment Procedures*, has been corrected by removing lateral views from bilateral lower extremity x-rays, and clarified to state that bilateral lower extremity x-rays, anterior-posterior (AP) view, are done to assess growth plate morphology. Instruction has been added to contact the medical monitor to discuss alternate non-radiological methods for assessment if there are IRBs or IECs unwilling to allow x-rays in Cohort 3 subjects (also, Table 9.1.1, footnote t). Additionally, the list of DXA acquisitions has been clarified.

w. Section 9.11.4.7.1, *Bayley-III*, has been revised to remove reference to the Social-Emotional and Adaptive Behavior Scale components because these scales will not be used in this study. Additionally, the duration of the assessment has been clarified.

x. In Section 9.11.4.7.4, *Child Behavior Checklist*, the duration of the assessment has been clarified.

y. In Section 10.1.2, the statement that hospitalization for less than 24 hours will not be considered an SAE has been deleted to make the criterion consistent across all BioMarin protocols. Section 10.1.2, *Serious Adverse Events*.

z. Error in Table 10.2.3.3.1 has been corrected to read “The AE could *not* be explained by factors or causes other than exposure to the IP”

2 SYNOPSIS

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

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

PROTOCOL NUMBER: 111-206

STUDY SITES: Approximately 10-15 sites worldwide

PHASE OF DEVELOPMENT: Phase 2

STUDY RATIONALE:

BMN 111 is a recombinant CNP analogue that has been engineered to resist degradation by NEP, allowing for a longer half-life.

The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ (TD) model (Lorget, 2012), and a milder [Ach] /+ (Ach) model. These included studies in 7-day old TD mice given BMN 111 daily by SC administration for up to 20 days and a study in 3-week old Ach mice given BMN 111 daily by SC administration for 5 weeks. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. In wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels (Wendt, 2015). Additionally, the potential effect of age on BMN 111 PK was evaluated in normal rats aged between 7 days and 12-13 weeks.

Infants and young children with ACH have a high incidence of medical complications and currently there is no approved pharmacological therapy for ACH in the US or EU. The most severe complication, cervicomedullary compression (CMC), occurs in a subset of subjects with ACH due to abnormal endochondral bone growth and narrowing of the foramen magnum (White, 2016). CMC has been linked to serious respiratory and neurological complications including hypotonia, apnea, ataxia, developmental delay, and respiratory arrest associated with sudden death (Mukherjee, 2014). Foramen magnum decompression surgery is currently the only treatment for this condition.

Sleep apnea has also been extensively described in ACH, and sleep-disordered breathing may affect up to 85% of all children with ACH (Ireland, 2012). This is thought to be due to midface hypoplasia, relative adenotonsillar hypertrophy, and potential posterior cranial fossa compression secondary to abnormal endochondral bone growth. Sleep apnea in ACH not only results in the need for surgical intervention, but has also been linked to sudden death in rare cases (Pauli, 1984).

Similarly, the dysregulation of endochondral bone growth in ACH leads to other medical complications which are prevalent in this subject population, such as the following:

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

- Spinal stenosis, kyphosis, and lordosis (secondary to altered growth plate ossification in the vertebrae and narrowing of the interpedicular distances) (Shirley, 2009)
- Developmental delay of gross motor and ambulatory skills (associated with proximal limb shortening, macrocephaly, and hypotonia) (Ireland, 2010)
- Delayed functional skills and increased need for caregiver assistance (eg, eating, bladder management, bowel management, transfer to chair, climbing stairs) (Ireland, 2011)

Thus, BMN 111 may provide greater benefit when children begin treatment at a younger age, as earlier initiation of treatment allows a longer time window to improve growth and potential to improve medical complications of achondroplasia. This study (111-206) is being conducted to assess safety and the potential benefit of BMN 111 in infants and young children.

BMN 111 was first tested in humans in Study 111-101, a Phase 1 double-blinded, placebo-controlled clinical trial of the safety and tolerability of BMN 111 in healthy adult male volunteers without ACH. Part 1 examined a series of single subcutaneous doses (5 µg/kg, 10 µg/kg and 15 µg/kg), and Part 2 included 10 days of either fixed dosing or dose escalation (0.5 µg/kg to 8 µg/kg). BMN 111 was generally well tolerated at all doses. As expected, mild, transient, self-limited hypotension was reported (refer to current Investigators Brochure for additional information). Following SC administration, BMN 111 was rapidly absorbed with maximal plasma concentrations achieved in less than 30 minutes. BMN 111 was rapidly cleared from the plasma with a mean $t_{1/2}$ ranging from 40 to 55 minutes across dose levels. BMN 111 exposure (C_{max} and AUC_{0-t}) generally increased greater than proportional to the increase in dose across the 2.5-to-15-µg/kg dose range. Exposure following multiple dosing was found to be similar to exposure following single doses, indicating no apparent accumulation or time-dependence with once-daily SC administration.

Study 111-202, the second clinical trial in humans and the first in children with ACH, is an ongoing Phase 2, open-label, sequential-cohort, dose-escalation study that assesses daily SC BMN 111 in pediatric subjects with ACH aged 5-14 years with doses ranging from 2.5 µg/kg to 30 µg/kg. The primary objective of Study 111-202 is to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months; the secondary objectives are to determine change from baseline in annualized growth velocity (AGV), growth parameters, body proportions, and evaluate the pharmacokinetics (PK) of BMN 111 in children with ACH.

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

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at the doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated (refer to current Investigator's Brochure for specific details). One subject (30 µg/kg) in 111-202 withdrew due to an AE. The subject developed non-serious, asymptomatic Grade 1 intermittent Wolff-Parkinson-White pattern, which was discovered on a routine day 10-study monitoring ECG. The most common AEs across all cohorts were injection site reactions, asymptomatic hypotension, headache, and nasopharyngitis. Based on previous experience of the ongoing Phase 2 clinical trial, including the 24-month data cut at 15 µg/kg, injection site reactions have been identified as risks associated with BMN 111 injections. The majority of hypotension events were grade 1 and reported in the setting of routine BP measurement. All reported events of hypotension were transient and resolved without medical intervention. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

Analysis of efficacy data from the 6-month initial phase of Study 111-202 showed that subjects treated with BMN 111 for 6 months at doses ranging from 2.5-15 µg/kg daily had a dose-dependent improvement in AGV, with ~50% improvement in AGV seen at the 15 µg/kg dose. The data from Cohort 4 (30 µg/kg) show an apparent greater than dose-proportional increase in BMN 111 plasma exposure (C_{max} and AUC_{0-t}), 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).

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are 0 to < 60 months old. This 52-week study will enable assessment of BMN 111 efficacy and safety, tolerability, pharmacodynamics biomarkers, and PK in this population. Additional exploratory endpoints pertaining to medical complications of ACH will also be evaluated.

Efficacy/toxicity studies have been conducted in neonatal and very young animals (7-day postpartum mouse and rat) in both a disease (TD mouse) and non-disease (rat) model. Given that this is the first study in infants and young children, an age-based cohort study design is used to assess safety and PK in young children (Cohort 1, ≥ 24 to < 60 months) prior to dosing toddlers (Cohort 2, ≥ 6 to < 24 months) and infants (Cohort 3, 0 to < 6 months). PK will be monitored and evaluated; Day 1 PK data from the sentinel subjects will inform dose selection modification for the sentinel subjects and for the rest of the cohort to target the observed exposure of the 15-µg/kg dose group in Study 111-202. Safety, efficacy and PK data from Study 111-202, a Phase 2 study in children with ACH, where a dose of 15 µg/kg has been and continues to be studied, are expected to be the most relevant, and translatable to this study (111-206).

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OBJECTIVES:

The primary objectives of the study are to:

- Evaluate the safety and tolerability of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate the effect of BMN 111 on change from baseline in length/height Z-score

The secondary objectives of the study are to:

- Evaluate the effect of BMN 111 on AGV throughout the 52 weeks of the study
- Evaluate the effect of BMN 111 on bone morphology/quality by x-ray and dual x-ray absorptiometry (DXA)
- Evaluate the PK of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of BMN 111 on developmental/functional/QOL status (Bayley-III, WeeFIM, Child Behavior Checklist [CBCL], ITQOL
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of BMN 111 on bone metabolism and BMN 111 pharmacodynamic biomarkers

The exploratory objectives of the study are to:

- Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower segment body ratio
- Evaluate the effect of BMN 111 on sleep apnea
- Document physical and phenotypic changes with clinical photography (optional)
- Evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

STUDY DESIGN AND PLAN:

This study, 111-206, is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH.

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Study 111-901 is an ongoing study to collect serial growth measurements on pediatric subjects with ACH who are being considered for subsequent enrollment in future BioMarin studies. Subjects age ≥ 6 months to < 60 months old who have documented ACH confirmed by genetic testing; at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry; and who meet the study eligibility criteria, will participate. Eligible subjects ranging from 0 months to < 3 months old may enroll directly into 111-206 and have a minimum of 3 months of pre-treatment observation prior to commencing treatment with investigational product, or may enroll in 111-901 for a minimum of 3 months of pretreatment growth assessment immediately before roll-over to 111-206.

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

The primary objectives of this study are to assess the safety and tolerability of daily SC BMN 111 administered to infants and young children with ACH, and to evaluate the effect of BMN 111 on length/height Z-score. Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive BMN 111, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who will be under observation or receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

If subjects who enroll in Cohort 3 are not able to begin treatment by <6 months of age, they will continue in the pretreatment period for another 3 months before enrolling in Cohort 2 to fulfill the pretreatment requirement for Cohort 2.

Sentinel subjects from each cohort will be enrolled, treated with BMN 111, and studied for short-term safety and PK data, after which subjects will be randomized to receive BMN 111 or placebo SC daily (1:1 ratio) for up to 52 weeks. No two sentinel subjects will be dosed on the same day for any cohort.

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At the start of the study, three sentinel subjects will be enrolled and monitored in Cohort 1. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data review, the weight-based dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 1 (≥ 27 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort (Cohort 2) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 2. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 2 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the youngest cohort (Cohort 3) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 3. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 3 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio).

Cohort 3 subjects must have a minimum of 3 months of observation prior to commencement of treatment. These subjects will have the option to enroll in either 111-901 or 111-206, depending on age at enrollment:

- Infants ≥ 3 months and < 6 months old (≥ 13 weeks and < 26 weeks) will enroll in 111-901 for a 6-month period of pretreatment growth assessment prior to enrollment in 111-206 for treatment in Cohort 2.
- Infants between birth and < 3 months old (0 weeks and < 13 weeks) will enroll into 111-206 with a 3-month observational period prior to treatment.

Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

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As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥24 to <60 months. Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in all treatment groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term; and to study the long-term outcomes on sustained growth, proportionality, bone maturation and medical comorbidities.

For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

Data Monitoring Committee (DMC)

In addition to safety and PK 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. After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort will be opened and the 3 sentinel subjects will be enrolled.

The DMC will make recommendations for stopping or continuing the study on an individual subject level and/or on a cohort level per the pre-specified stopping criteria. Based on criteria outlined in the protocol, the DMC may also make endorsements for dose adjustments if needed.

Please see DMC Charter for further details.

Individual Subject Stopping Criteria

For individual subjects treated with BMN 111, DMC will be informed if any of the following individual subject stopping criteria should occur. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the individual subject will be considered.

- Any treatment-emergent adverse event (AE) assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (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

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- Clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec
- Clinically significant new or worsening signs of cervicomedullary compression as determined by the Investigator and in consultation with Sponsor medical monitor and neurosurgical specialist (if needed)
- Adverse findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as determined by the Investigator and in consultation with Sponsor Medical Monitor and orthopedic specialist (if needed)

If the subject meets any stopping criterion, 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 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
- Permanent treatment discontinuation (with an option of ongoing assessment in the study)

Cohort Stopping Criteria

For each cohort, a DMC review will be conducted if any of the following cohort stopping criteria occur in subjects treated with BMN 111. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the cohort(s) will be considered and the impact on all other age cohorts will be assessed.

- Any treatment-emergent AE assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have a treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any two subjects cohort have a Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Any two subjects have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec

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- Any two subjects have adverse 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)

Dose Adjustments

Analysis of available PK data from studies 111-101 and 111-202 indicated that differences in subject body weight did not directly translate to differences in total body clearance of BMN 111. The same weight-based dose in the pediatric population of Study 111-202 (5-12 years old) yielded lower exposure (C_{max} and AUC) than that characterized in the adult population of Study 111-101. Therefore, the same weight-based dose in the young pediatric population in this study may yield exposure less than the target exposure range characterized to be safe and effective in Study 111-202 at the 15-µg/kg dose. Since this is the first experience with BMN 111 in this young pediatric population, it is also possible the exposure at 15 µg/kg could be greater than the target exposure range, and dose adjustment may be warranted. Thus, an option for adjustment of the weight-based dose is provided to ensure that the appropriate target exposure for safety and efficacy is reached for the young subjects in this study.

The need for dose adjustment will be evaluated as follows: three sentinel subjects in Cohort 1 will receive an initial dose of 15 µg/kg. After all three sentinel subjects reach Day 8, a review will occur to evaluate all available safety and PK data (at minimum). If the criteria for dose adjustment are met, the three sentinel subjects will be started on the new adjusted dose at their next scheduled visit, and vital signs will be obtained for at least 4 hours post-dose.

The remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. After the third sentinel subject reaches Week 12 post-dose adjustment, a DMC review will occur to evaluate all safety and PK data and, upon endorsement, the three sentinel subjects from the next younger cohort will be enrolled starting at the new adjusted dose. The three sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥ 24 to < 60 months.

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Safety and Efficacy Monitoring

Each treated subject will have expanded outpatient safety monitoring for a minimum of 3 days of dosing, during which they will be closely observed and non-invasive hemodynamic monitoring will be conducted for at least 4-8 hours post-dosing. Because younger children may not be able to verbalize complaints of dizziness or lightheadedness that are potentially associated with hypotension, study personnel and caregivers will be trained to recognize the signs of hypotension in this population, which may include tachycardia, pallor, diaphoresis, lethargy, delayed capillary refill, and poor feeding. Appropriate rigorous training will be required for parents and caregivers prior to daily injections at home. Training includes the storage, reconstitution, and administration of BMN 111, as well as documentation/reporting of AEs and vigilance for signs of hypotension.

It is generally expected that after subjects are tolerating the drug well and specified criteria have been met, caregivers will begin administering study drug. Home health care is not required at any point but may be provided if the caregiver is unable or unavailable to administer the study drug. A Home Healthcare nurse will train the caregiver(s) if training has not been completed by the Day 3 visit. A phone call by the study staff member to the caregiver will be required weekly for 6 months and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. If the caregiver cannot be contacted by phone after two attempts, contact can be made via email.

Safety will be evaluated by the incidence of AEs, serious AEs (SAEs), laboratory test results (urinalysis, chemistry, and hematology), vital signs, physical examination, ECG and echocardiogram, hip clinical assessment, and anti-BMN 111 immunogenicity assessments. Clinical laboratory tests, PK, immunogenicity and blood biomarker assessments will be limited to the minimum necessary for evaluation of safety and efficacy in order to minimize blood volume in the pediatric population.

Efficacy will be assessed by change from baseline in AGV and length/height Z-score. Exploratory assessments will include change from baseline in growth parameters and body proportions by anthropometry. X-rays will be performed of the lower extremities and spine to evaluate for changes in bone morphology, quality, and growth. An MRI will be performed to assess the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions. A board-certified, fellowship-trained (or equivalent) pediatric anesthesiologist will administer anesthesia during MRI measurements in the event that the subject is unable to remain still for the duration of the scan. Sleep studies will be conducted to evaluate sleep apnea. Additional assessments will be conducted to evaluate changes from baseline in bone metabolism and BMN111 pharmacodynamic biomarkers, and developmental/functional status.

NUMBER OF SUBJECTS PLANNED: Approximately 70 subjects, including at least 30 subjects in Cohort 1, at least 20 subjects in Cohort 2, and at least 20 subjects in Cohort 3.

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DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Diagnosis of ACH, confirmed by genetic testing. If subjects had previous genetic testing, subjects must have a lab report from a certified laboratory with the study specific mutation documented.
2. Age 0 to < 60 months, at study entry (Day 1)
3. Cohort 1 and 2 subjects must have at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry and have one documented measurement of height/body length a minimum of 6 months (+/- 10 days) prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrollment in Study 111-901 or (2) via enrollment in this Study 111-206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment.
4. Parent(s) or guardian(s) (and the subjects themselves, if required by local regulations or ethics committee) 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
5. Willing and able to perform all study procedures as physically possible
6. Parent(s) or caregiver(s) are willing to administer daily injections to the subjects and complete the required training

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

1. Have hypochondroplasia or short-stature condition other than achondroplasia (e.g., trisomy 21, pseudoachondroplasia, etc.)
2. Subject weighs < 5.0 kg (Cohorts 1 and 2) or < 4.0 kg (Cohort 3)
3. Have any of the following:
    - Hypothyroidism or hyperthyroidism
    - Insulin-requiring diabetes mellitus
    - Autoimmune inflammatory disease (including celiac disease, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, etc.)
    - Inflammatory bowel disease
    - Autonomic neuropathy

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4. Have a history of any of the following:

- Renal insufficiency defined as serum creatinine > 2 mg/dL
- Chronic anemia or Hgb < 10.0 g/dL (based on screening clinical laboratory testing)
- Baseline systolic blood pressure (BP) below age and gender specified normal range or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms e.g., dizziness, fainting) or recurrent symptomatic orthostatic hypotension
- Cardiac or vascular disease, including the following:
    - Cardiac dysfunction (abnormal echocardiogram determined to be clinically significant by PI and medical monitor) at Screening Visit
    - Hypertrophic cardiomyopathy
    - Pulmonary hypertension
    - Congenital heart disease with ongoing cardiac dysfunction
    - Cerebrovascular disease
    - Aortic insufficiency or other clinically significant valvular dysfunction
    - Clinically significant atrial or ventricular arrhythmias

5. Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening ECG

6. Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator and informed by the following assessments:

    - Physical exam (eg, neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins)
    - Polysomnography (eg, severe central sleep apnea)
    - MRI indicating presence of severe CMC or spinal cord damage

7. Have an unstable medical condition likely to require surgical intervention in the next 6 months, or planned spine or long-bone surgery (i.e., surgery involving significant disruption of bone cortex) during the study period

8. Have documented uncorrected Vitamin D deficiency: 25(OH)D ≤ 15 ng/mL (37.5 nmol/L)

9. Require any other investigational product prior to completion of the study period

10. Have received another investigational product or investigational medical device within 30 days prior to the Screening visit

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11. Have used any other investigational product or investigational medical device for the treatment of achondroplasia or short stature at any time
12. Require current chronic therapy with antihypertensive medication or any medication that, in the investigator's judgment, may compromise the safety or ability of the subject to participate in this clinical study (Table 9.3.5.1)
13. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (> 3 months) at any time
14. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the 12 months prior to screening
15. Have ever had cervicomedullary decompression surgery (Cohorts 2 and 3 only), spine or long-bone surgery (ie, surgery involving disruption of bone cortex) or have ever had bone-related surgery with chronic complications

    NOTE: Subjects with prior cervicomedullary decompression may be allowed into Cohort 1 only after discussion and agreement with Medical Monitor.
16. Have ever had limb-lengthening surgery or plan to have limb-lengthening surgery during the study period
17. Have had a fracture of the long bones or spine within 6 months prior to screening
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin greater than upper limit of normal at screening (except for subjects with a known history of Gilberts or newborns entering screening in Cohort 3)
19. Have evidence of severe untreated sleep apnea; or have newly initiated sleep apnea treatment (eg, CPAP or sleep apnea-mitigating surgery) in the 2 months prior to screening
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 history of hip surgery or severe hip dysplasia
23. Have a history of clinically significant hip injury in the 30 days prior to screening
24. Have a history of slipped capital femoral epiphysis or avascular necrosis of the femoral head

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25. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the Investigator
26. 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
27. Have any concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, for any reason

Inclusion Criteria for Cohort 3 Observation Period

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

1. Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, willing and able to provide written assent (if applicable) after the nature of the study has been explained and prior to performance of any research-related procedure.
2. Birth to ≤ 3 months of age at study entry.
3. Have ACH, documented by genetic testing
4. Are willing and able to perform all study procedures as physically possible

Exclusion Criteria for Cohort 3 Observation Period

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 disorders:
    - Hypothyroidism
    - Insulin-requiring diabetes mellitus
    - Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others)
    - Inflammatory bowel disease
    - Autonomic neuropathy
3. Have an unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression

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4. Have a history of any of the following:
    - Renal insufficiency
    - Anemia
5. Have a history of cardiac or vascular disease, including the following:
    - Cardiac dysfunction
    - Hypertrophic cardiomyopathy
    - Congenital heart disease
    - Cerebrovascular disease, aortic insufficiency
    - Clinically significant atrial or ventricular arrhythmias
6. Current treatment 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, drugs known to alter renal function that is expected to continue for the duration of the study
7. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable) in the previous 3 months
8. Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
9. Have used any other investigational product or investigational medical device for the treatment of ACH or short stature
10. Planned or expected bone-related surgery (ie. surgery involving disruption of bone cortex), during the study period.
11. Planned or expected to have limb-lengthening surgery during the study period.
12. Have any condition that, in the view of the Investigator, places the subject at high risk of poor compliance with the visit schedule or of not completing the study.
13. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation

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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 a 0.8-mg or 2-mg lyophilized, preservative-free, white-to-yellow powder for reconstitution with either a sterile diluent or sterile water for injection. The reconstituted solution is colorless to yellow and contains 0.8 mg/mL to 2 mg/mL of BMN 111, as well as citric acid, sodium citrate, trehalose, mannitol, methionine, polysorbate 80, and sterile water for injection. The target pH of the reconstituted solution is 5.5. Sterile water for injection will be commercially sourced and sterile diluent solution containing all of the above excipients will be supplied for reconstitution. All reconstitution and dose preparation steps will be performed as indicated in the BMN 111 Injection Guide and Injection video.

BMN 111 will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic.

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

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

Placebo will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic.

DURATION OF TREATMENT: Up to 52 weeks

CRITERIA FOR EVALUATION:

Safety: The following safety outcome measurements will be assessed:

- Incidence of AEs and SAEs
- Vital signs (heart rate, blood pressure, respiratory rate, and temperature)
- Physical examination (including neurological assessment)
- Hip clinical assessment
- Laboratory test results (urinalysis, chemistry, hematology)
- Electrocardiogram (ECG)

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- Echocardiogram
- Anti-BMN 111 immunogenicity assessments
- Cortisol levels
- Prolactin levels

Efficacy: The following efficacy outcome measurements will be assessed:

- Change from baseline in AGV
- Change from baseline in length/height Z-score

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

Drug accumulation after repeat-dose administration will also be evaluated. PK parameters at Week 13, 26, 39 and 52 will be compared to Day 1. The impact of immunogenicity (if present) on PK will also be evaluated.

Bone metabolism and BMN 111 pharmacodynamic biomarkers:

- Changes in bone and collagen metabolism and BMN 111 activity will be assessed.

Clinical outcome assessments:

- Bayley-III
- WeeFIM
- CBCL
- ITQOL

Exploratory: The following exploratory measurements will be assessed:

- Upper:lower body segment ratio
- Imaging assessments (X-rays of the spine and lower extremities)
- MRI to define skull and brain morphology (including dimensions of foramen magnum, ventricular and brain parenchymal dimensions)
- Sleep study
- Clinical photography (optional)

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

STATISTICAL METHODS:

Sample Size Determination: Approximately 70 subjects age 0 to < 60 months at study entry will participate in this study. No formal sample size calculations were performed. The number of subjects is considered appropriate to evaluate the safety and efficacy of BMN 111 in the target population.

Safety Analysis: All subjects who receive at least one dose of study treatment or who are randomized to the placebo-control group in this study will be included in the safety analysis. The safety analysis will be descriptive.

All AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) to assign system organ class and preferred term classification to event and disease, based on the original terms entered on the eCRF. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment as assessed by the investigator, seriousness, 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, echocardiogram, hip clinical assessment, and concomitant medication data will also be summarized descriptively. Data summaries will be presented by treatment group (when applicable) for each cohort and overall. All safety results will be listed.

Efficacy Analysis:

All randomized subjects who receive at least one dose of study treatment or placebo in the study will be included in the efficacy analysis.

Efficacy variables, including AGV (based on length/height) and length/height Z-score according to normal reference standards (not ACH), along with their change from baseline will be summarized by treatment group and cohort. Comparisons between treatment groups by cohort on these variables will be carried out where appropriate. Statistical comparisons will be considered descriptive. 95% CIs will be provided along with p values for treatment group comparisons.

Sentinel subjects will be summarized apart for both efficacy and safety.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

°C	degree Celsius
ACE	angiotensin-converting enzyme
Ach	Fgfr3G380R achondroplasia mouse model
ACH	achondroplasia
ADL	Activity of Daily Living
ADR	adverse drug reaction
AE	adverse event
AGV	annualized growth velocity
ALT	alanine aminotransaminase
ANP	atrial natriuretic peptide
AP	anterior-posterior
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMC	bone mineral content
BMD	bone mineral density
BNP	B-type Natriuretic Peptide
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
C_{max}	maximum observed plasma concentration
CBCL	Child Behavior Checklist
CNP	C-type natriuretic peptide
CNP53	C-type natriuretic peptide (53 amino acids in length)
CRA	clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DCF	data clarification form
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FGF	fibroblast growth factor
G380R	substitution in the transmembrane domain of the FGFR3 receptor at position 380
GCP	Good Clinical Practice

HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRQOL	health-related quality of life
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICH E6 [R2]	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	Independent ethics committee
IgE	immunoglobulin E
IND	Investigational New Drug (application)
IP	investigational product
IRB	institutional review board
ITQOL	Infant Toddler Quality of Life questionnaire
LV	left ventricular
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
msec	millisecond
NAb	neutralizing antibodies
NEP	neutral endopeptidase
NP	natriuretic peptide
NPR-B	natriuretic peptide receptor type B
PA	posterior-anterior
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
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
REB	research ethics board
rhCNP	recombinant C-type natriuretic peptide
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOI	Statement of Investigator Form
$t_{1/2}$	elimination half-life
TAb	total antibody

Tmax	time to reach C_{max}
ULN	upper limit of normal
US	United States
WeeFIM	Functional independence measure for children
WFI	water for injection
µg/kg	microgram/kilogram

Definition of Terms:

Investigational Product (IP):

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6] (R2)]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated for subjects who do not speak the local language at 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/IEC/REB confirming unconditional approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the Investigator and copies are received at BioMarin or its designee. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the study are made to the IRB/IEC/REB and BioMarin by the Investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

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

This study will be conducted in accordance with the following:

- European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, for studies conducted within any European country
- 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) or E6(R2) (ICH E6R2) if adopted
- The ethical principles established by the Declaration of Helsinki

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

5.3 Subject Information and Informed Consent

A properly written and executed informed consent form (ICF), in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, 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/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF (minor assent form and parental ICF for studies involving minors), and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

6 INVESTIGATORS AND STUDY ADMINSTIRATIVE 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 Statement of Investigator (SOI) form. A US Food and Drug Administration (FDA) Form FDA 1572 serves as an acceptable SOI form. If Form FDA 1572 may not be used in a particular region, the Investigator must provide a fully executed SOI on the form provided by the Sponsor. All Investigators and Sub-Investigators must be listed on Form FDA 1672 or its equivalent SOI. Financial Disclosure Forms must also be completed for all Investigators and Sub-Investigators listed on the Form FDA 1572 or SOI who will be directly involved in the treatment or evaluation of subjects in this study.

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

In multicenter studies, 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.

7 INTRODUCTION

BMN 111 is a proposed pharmacologic 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) The average adult heights for men and women with ACH are 131 cm and 124 cm, respectively (NIH, Genetics Home Reference, 2012). Characteristic features include long and narrow trunk, a large head with frontal bossing, hypoplasia of the mid-face, bowed legs and stenosis of the foramen and spinal canals that can be life-threatening. Foramen magnum stenosis can lead to cervicomedullary compression in infants with complications including hydrocephalus, hypotonia, respiratory insufficiency, apnea, cyanotic episodes, feeding problems, quadriparesis, and sudden death.

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

ACH is caused by a gain-of-function mutation in 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.

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

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

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

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

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

7.1 Nonclinical Studies

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

BMN 111-related adverse findings in nonclinical species (mice, rats, cynomolgus monkeys) were limited to the known mechanism of action of CNP on the growth plate and vasculature. Reversible subcutaneous injection site reactions were reported, including injection site discoloration and microscopic findings of perivascular mononuclear cell infiltrates that were seen with slightly higher incidence and severity in BMN 111-treated rats and monkeys compared to the vehicle control. Adverse skeletal changes associated with exaggerated growth were seen in normal nonclinical species with open growth plates, and were dose-, exposure- and time-dependent. Decreases in blood pressure and compensatory increases in heart rate were detected in monkeys across multiple studies, with overt CV-related clinical signs observed in some animals at doses $\geq$ 236 µg/kg. These overt clinical signs consisted of transient, short and repeated bouts of sternal or lateral recumbency and/or reduced motor activity, typically within 1-hour post-dose administration. Additional detailed information

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

7.2 Previous Clinical Studies

7.2.1 Study 111-101

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

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

The PK parameters for BMN 111 were obtained from Part 1 of the study and from the first dose on Day 1 of the multiple dose study in Part 2. The results demonstrate that BMN 111 was rapidly absorbed in human, reaching a mean time to peak concentration (T_{max}) between 15-26 minutes. After reaching maximal plasma concentrations, BMN 111 levels rapidly declined, with a $t_{1/2}$ of 40-55 minutes. Mean plasma concentration-time profiles indicate that exposure increased with dose from 2.5 to 15 µg/kg. The corresponding increases in plasma C_{max} and area under the curve (AUC) exposure parameters were greater than dose proportional. The increase in C_{max} with dose was linear over the dose range evaluated. In Part 2, with multiple dosing at 5 µg/kg for 10 days, the plasma concentration-time curves obtained on each of the three sampling days were nearly superimposable. Comparison of PK exposure parameters for AUC and C_{max} indicate that C_{max} is unchanged and AUC is

increased slightly by +33% over Day 1. Overall the results indicate that changes in BMN 111 exposure are minimal with repeat dosing out to 10 days.

7.3 Ongoing Clinical Studies

7.3.1 Study 111-901

Study 111-901 is a multicenter, multinational study to collect serial growth measurements on pediatric subjects with ACH who are being considered for subsequent enrollment in future studies sponsored by BioMarin. To obtain accurate baseline measurements, at least 6 months of growth data are collected.

Data gathered from this study are used to characterize baseline growth data in children or infants (defined as children < 2 years of age) who may subsequently be enrolled in future studies sponsored by BioMarin, and may also be used to establish historical control cohort for use in other BioMarin-sponsored studies, when appropriate. For that reason, data related to ACH symptoms, tests, and interventions are collected.

7.3.2 Study 111-202

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

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

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

For longer term follow up data from the 202 study, please refer to the current Investigator Brochure supplied by BioMarin.

7.3.3 Study 111-205

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

7.3.4 Study 111-301

Study 111-301 is an ongoing Phase 3, double-blind, placebo-controlled multicenter study to further characterize and confirm efficacy and safety of BMN 111 at 15 µg/kg in a 58-week study (up to 4 weeks of screening, 52 weeks of treatment, plus an additional 2 weeks of safety follow up). The study assesses the effect of daily BMN 111 administration on change from baseline in AGV, height, and body proportions in subjects treated with BMN 111 compared with control subjects in the placebo group; and further characterizes safety and tolerability of BMN 111 in children with ACH. Additional exploratory endpoints are being examined to determine the effect of BMN 111 on bone physiology and to assess quality of life and daily function of study subjects.

7.3.5 Study 111-302

Study 111-302 is an open-label Phase 3 extension study to further evaluate the efficacy and safety of BMN 111 either until subjects reach near-final adult height (defined as evidence of growth plate closure and < 1.5 cm/yr annualized growth velocity), or for 5 years if near-final adult height (NFAH) occurs prior to the end of the 5-year period. All subjects will receive BMN 111 15 µg/kg. This study will allow for long-term assessment of the effect of daily BMN 111 administration on safety, tolerability, growth velocity, height, and body proportions in subjects who have completed 1 year of placebo or BMN 111 treatment in Study 111-301.

7.4 Study Rationale

BMN 111 is a recombinant CNP analogue that has been engineered to resist degradation by NEP, allowing for a longer half-life.

The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ (TD) model (Lorget, 2012), and a milder [Ach] /+ (Ach) model. These included studies in 7-day old TD mice given BMN 111 daily by SC administration for up to 20 days and a study in 3 week old Ach mice given BMN 111 daily by SC administration for 5 weeks. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. In wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels (Wendt, 2015). Additionally, the potential effect of age on BMN 111 PK was evaluated in normal rats aged between 7 days and 12-13 weeks.

Infants and young children with ACH have a high incidence of medical complications and currently there is no approved pharmacological therapy for ACH in the US or EU. The most severe complication, cervicomedullary compression (CMC), occurs in a subset of subjects with ACH due to abnormal endochondral bone growth and narrowing of the foramen magnum (White, 2016). CMC has been linked to serious respiratory and neurological complications including hypotonia, apnea, ataxia, developmental delay, and respiratory arrest associated with sudden death (Mukherjee, 2014). Foramen magnum decompression surgery is currently the only treatment for this condition.

Sleep apnea has also been extensively described in ACH, and sleep-disordered breathing may affect up to 85% of all children with ACH (Ireland, 2012). This is thought to be due to midface hypoplasia, relative adenotonsillar hypertrophy, and potential posterior cranial fossa compression secondary to abnormal endochondral bone growth. Sleep apnea in ACH not only results in the need for surgical intervention, but has also been linked to sudden death in rare cases (Pauli, 1984).

Similarly, the dysregulation of endochondral bone growth in ACH leads to other medical complications which are prevalent in this subject population, such as the following:

- Spinal stenosis, kyphosis, and lordosis (secondary to altered growth plate ossification in the vertebrae and narrowing of the interpedicular distances) (Shirley, 2009)
- Developmental delay of gross motor and ambulatory skills (associated with proximal limb shortening, macrocephaly, and hypotonia) (Ireland, 2010)

- Delayed functional skills and increased need for caregiver assistance (eg, eating, bladder management, bowel management, transfer to chair, climbing stairs) (Ireland, 2011)

Thus, BMN 111 may provide greater benefit when children begin treatment at a younger age, as earlier initiation of treatment allows a longer time window to improve growth and potential to improve medical complications of achondroplasia. This study (111-206) is being conducted to assess safety and the potential benefit of BMN 111 in infants and young children.

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

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

Study 111-202 is an ongoing Phase 2, open-label, sequential cohort, dose escalation study that assesses daily SC administration of BMN 111 in pediatric subjects with ACH, in which the primary objective is to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months and includes secondary objectives consisting of determination of change from baseline in AGV, growth parameters, body proportions, and evaluation of the dose-exposure and PK profiles of BMN 111 in children with ACH.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 was generally well tolerated at all dose levels (refer to current Investigators Brochure for specific details).

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

Subjects treated with 30 µg/kg daily also showed similar improvement in mean AGV after 6 months and their mean changes from baseline in AGV were similar to subjects treated with

15 µg/kg daily. Safety data for the 30-µg/kg daily dose was also similar to the 15-µg/kg daily dose. Given that no clinically significant difference could be identified between the 15-µg/kg and 30-µg/kg daily dose in the Phase 2, 6-month safety and efficacy data, the lower of the two doses has been chosen for this Phase 2 study.

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are age 0 to < 60 months. This 52-week study will enable assessment of BMN 111 safety, tolerability, pharmacodynamics biomarkers, and PK in this population, and also allow for examination of potential impact on efficacy endpoints. Additional exploratory endpoints pertaining to medical complications of ACH will also be evaluated.

7.5 Summary of Overall Risks and Benefits

7.5.1 Summary of Risks from Nonclinical Studies

Individuals in this study will be exposed to a recombinant analogue of human C-type natriuretic peptide (CNP). Based on the results of experimentation in animals, the most relevant potential toxicities relate to the expected pharmacological effects of exogenous CNP administration, including hemodynamic changes, skeletal overgrowth, and injection site reactions. Transient and sporadic decreases in blood pressure and compensating increases in heart rate occurred within the first hour post-dose in cynomolgus monkeys; the effects were mainly asymptomatic with a subset of animals given doses ≥ 236 µg/kg observed with symptomatic effects consisting of transient, short and repeated bouts of sternal or lateral recumbency and/or reduced motor activity. These hemodynamic effects can be monitored, but have the potential to be an acute dose-limiting factor in patients. Exaggerated appendicular bone responses to the drug included abnormally shaped femoral head, acetabular growth center/plate dysplasia and concomitant articular cartilage degeneration with clinical manifestations of restricted use of hips. Adverse skeletal changes associated with exaggerated growth were dose-, exposure- and time-dependent. Additional detailed information about risks identified in nonclinical studies of BMN 111 is provided in the current version of the Investigator's Brochure supplied by BioMarin.

7.5.2 Summary of Risks from Clinical Studies

7.5.2.1 Study 111-101

Based on review of the first-in-human Phase 1 study of BMN 111 in healthy adult volunteers, Study 111-101, BMN 111 administered SC daily was well tolerated with doses ranging from 0.5 µg/kg to 15 µg/kg. All AEs were of mild severity, and no SAEs were reported. The most common AE was mild, transient, self-limited orthostatic hypotension, of which the majority

of cases were asymptomatic and observed only upon assumption of an upright posture following recumbence. No dose-limiting toxicities were identified outside of these CV events.

7.5.2.2 Ongoing Studies

Based on analysis of safety data from ongoing phase 2 and 3 studies, treatment with BMN 111 was generally well tolerated. Injection site reactions were the most common adverse events reported and are considered to be an identified risk. All injection site reactions events have been reported as non-serious, Grade 1 in severity, and transient. Hypotension and hypersensitivity reactions including development of BMN 111 antibodies are potential risks associated with BMN 111 injections. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

7.5.3 Summary of Potential Benefits from Clinical Studies

For children with ACH who will receive BMN 111 as part of Study 111-206, potential benefits may include improvement of AGV rates such that their increase in growth velocity may approach that of children of average stature. Additional potential benefits may include improvement of the disproportionate growth as well as improvement in quality of life, activities of daily living, and medical complications of ACH. For example, improvement in height could have an impact on daily activity performance.

8 STUDY OBJECTIVES

The primary objectives of the study are to:

- Evaluate the safety and tolerability of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate the effect of BMN 111 on change from baseline in length/height Z-score

The secondary objectives of the study are to:

- Evaluate the effect of BMN 111 on AGV throughout the 52 weeks of the study
- Evaluate the effect of BMN 111 on bone morphology/quality by x-ray and dual x-ray absorptiometry (DXA)
- Evaluate the PK of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of BMN 111 on developmental/functional/QOL status (Bayley-III, WeeFIM, Child Behavior Checklist [CBCL], ITQOL
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of BMN 111 on bone metabolism and BMN 111 pharmacodynamic biomarkers

The exploratory objectives of the study are to:

- Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower body segment ratio
- Evaluate the effect of BMN 111 on sleep apnea
- Document physical and phenotypic changes with clinical photography (optional)
- Evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH.

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

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

The primary objectives of this study are to assess the safety and tolerability of daily SC BMN 111 administered to infants and young children with ACH, and evaluate the effect of BMN 111 on Z-scores. Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive BMN 111, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

If subjects who enroll in Cohort 3 are not able to begin treatment by < 6 months of age, they will continue in the pretreatment period for another 3 months before enrolling in Cohort 2 to fulfill the pretreatment requirement for Cohort 2.

Sentinel subjects from each cohort will be enrolled and studied for short-term safety and PK data, after which subjects in all 3 cohorts will be randomized to receive BMN 111 or placebo SC daily (1:1 ratio) for up to 52 weeks. No two sentinel subjects will be dosed on the same day for any cohort. At the start of the study, 3 sentinel subjects will be enrolled and monitored in Cohort 1. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 1 (≥ 27 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort (Cohort 2) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 2. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 2 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the youngest cohort (Cohort 3) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 3. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 3 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio).

Cohort 3 subjects must have a minimum of 3 months of observation prior to commencement of treatment. These subjects will have the option to enroll in either 111-901 or 111-206, depending on age at enrollment:

- Infants ≥ 3 months and < 6 months old (≥ 13 weeks and < 26 weeks) will enroll in 111-901 for a 6-month period of pretreatment growth assessment prior to enrollment in 111 206 for treatment in Cohort 2.

- Infants between birth and < 3 months old (0 weeks and < 13 weeks) will enroll into 111-206 with a 3-month observational period prior to treatment.

Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥ 24 to < 60 months.

Each treated subject will have expanded outpatient safety monitoring for a minimum of 3 days of dosing, during which they will be closely observed and non-invasive hemodynamic monitoring will be conducted for at least 4-8 hours post-dosing. Because younger children may not be able to verbalize complaints of dizziness or lightheadedness that are potentially associated with hypotension, study personnel and caregivers will be trained to recognize the signs of hypotension in this population, which may include tachycardia, pallor, diaphoresis, lethargy, delayed capillary refill, and poor feeding. Appropriate rigorous training will be required for parents and caregivers prior to daily injections at home. Training includes the storage, reconstitution, and administration of BMN 111, as well as documentation/reporting of AEs and vigilance for signs of hypotension.

It is generally expected that after subjects are tolerating the drug well and specified criteria have been met, caregivers will begin administering study drug. Home health care is not required at any point but may be provided if the caregiver is unable or unavailable to administer the study drug. A Home Healthcare nurse will train the caregiver(s) if training has not been completed by the Day 3 visit. A phone call by the study staff member to the caregiver will be required weekly for 6 months and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. If the caregiver cannot be contacted by phone after two attempts, contact can be made via email.

Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in all treatments groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term. For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

A summary of events and assessments are provided by visit in Table 9.1.1 and Table 9.1.2.

For a discussion of efficacy assessments, see Section 9.11.2 and Section 9.11.3; exploratory efficacy assessments, Section 9.11.4; safety assessments, Section 9.11.6; and PK variables, Section 9.11.5. The 111-206 study design is presented in Figure 9.1.1.

Figure 9.1.1: Study Design

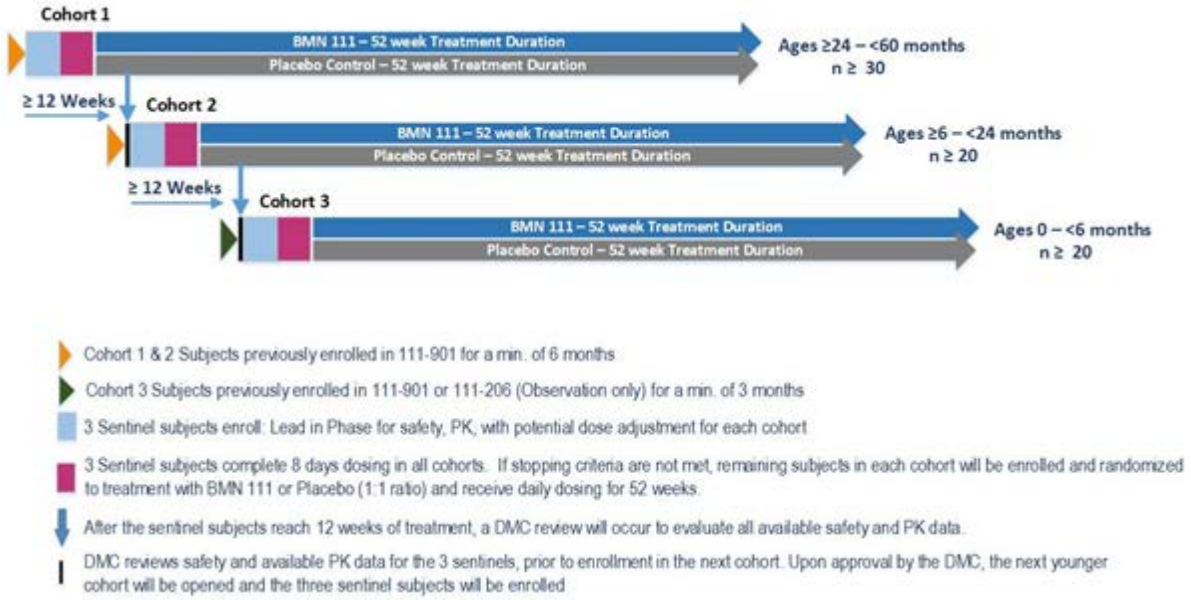


Table 9.1.1: Schedule of Events

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1[u]	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (+7d)[z]	Early Term Visit
Informed consent	X													
Medical history[c]	X													
Parental height[d]	X													
Diagnostic genetic testing to confirm achondroplasia (if needed)[e]	X													
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[h]	X	X			X		X	X	X	X	X	X	X	X
Echocardiogram[i]	X												X	X[i]
Anthropometric measurements[j]	X	X					X	X		X	X	X		X
Clinical laboratory assessments (hematology, chemistry, urinalysis)[k]	X				X	X	X		X		X	X		X
Thyroid function tests	X											X		
Vitamin D, 25-hydroxy test	X											X		
Salivary cortisol	X									X		X		X
Serum prolactin	X									X		X		X
Plasma pharmacokinetics and cGMP assessments[l]		X						X		X	X	X		
Anti-BMN 111 immunogenicity[m]		X				X		X		X		X		X

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1[u]	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (+7d)[z]	Early Term Visit
Genomic biomarkers (optional)							X					X		
Bone metabolism blood biomarkers[n]	X				X		X		X		X			X
Bone metabolism urine biomarkers[o]		X	X	X		X		X		X	X	X		X
BMN 111 pharmacodynamic urine biomarkers[o]		X	X	X		X		X		X	X	X		X
Urine chemistry[o]		X	X	X		X		X		X	X	X		X
Screening baseline hip assessment with pelvis x-ray	X													
Hip monitoring[p]										X		X		X
MRI brain/skull[q]	X											X		X
Sleep study[r]	X											X		X
Clinical outcome assessment: Bayley-III	X									X		X		X
Clinical outcome assessment: WeeFIM[s]	X									X		X		X
Clinical outcome assessment: ITQOL	X									X		X		X
Clinical outcome assessment: CBCL[s]	X									X		X		X
DXA (BMD and BMC) of whole body [less head], spine and forearm (including ultra-distal,mid-distal, and one	X											X		X

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1[u]	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (+7d)[z]	Early Term Visit
mid-distal, and one third radius regions of interest)														
AP and lateral X-rays of spine[t]	X											X		X
AP X-rays of lower extremities[t]	X											X		X
Clinical photographs (optional)[u]	X											X		X
Capture all procedures in the Schedule of Events		X	X	X	X	X	X	X	X	X	X	X	X	X
BMN 111 or placebo administration[v]		All visits												
BMN 111 or placebo accountability		All visits												X
Adverse events[w]		All visits											X	X
Concomitant medications[x]	X	All visits											X	X
Phone call or home health visit[y]		Weekly calls for 6 months and then every 2 weeks for the remainder of the study												

[a] Clinic visits (except Days 1, 2, 3, and 8) have a ± 7-day window. Anthropometric measurement and imaging assessments can be conducted either pre-dose or post-dose.

[b] If the 111-901 visit at which the subject enters Study 111-206 and the 111-206 Screening visit are on the same day, the procedures common to both visits will be performed one time only. All blood tests at Screening visit should be obtained between Day -30 and Day -14.

[c] 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.

[d] 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, the parent can provide their stated height instead if consent has been given.

[e] If subjects had previous genetic testing, subjects must have a lab certification documenting the specific mutation required for the 111-206 study, including the identification of FGFR3 mutation (G346E, G375C, G380R, or "other").

[f] Complete physical exam includes 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.

[g] 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, BP, and respiratory rate.

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

1. Vital sign measurements are taken once per time point, preferably in a sitting or supine position, after at least 5 minutes of rest.
2. Heart rate, blood pressure, and respiratory rate should be taken and recorded at each indicated time point.
3. When blood samples and vital sign assessments are scheduled at the same time or within the same time window, vital signs should be measured before blood samples are drawn.
4. If a vital sign measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and wait several minutes before measuring vital signs.
5. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
6. If a subject has a hypotensive event, or signs potentially consistent with hypotension, or a decrease of 20 mm Hg systolic BP or more from baseline (defined by pre-dose vitals collected that day), vital signs should be measured and recorded approximately every 15 minutes (± 5 minutes) for the first hour and every 30 minutes (± 5 minutes) thereafter until the BP returns to baseline (or within the normal range for this subject as defined by PI) and signs (if present) resolve.
7. If the decision is made to adjust the dose, vital signs will be obtained for at least 4 hr following the first dose at the adjusted dose level, similar to the Day 3, 8 schedule.
8. If a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1,2 schedule.

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

[i] Echocardiogram is obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination.

[j] Growth measures may be collected in triplicate 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 length, standing height (if able to stand unsupported), crown-to-rump length, head circumference, upper and lower arm and leg, and arm span. Measurements not taken in the midsagittal plane should be taken on the right side of the body if possible and should always be taken on the same side of the body throughout the study.

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

[l] Plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes. Samples with volume remaining after pharmacokinetic assessment will be used for cGMP pharmacodynamics assessment. NOTE: In the event of interruption of study drug administration for a sentinel patient on Day 1 when PK samples are scheduled, the collection of PK samples should be delayed until the subsequent day and only performed after successful administration of study drug has been completed in a single injection.

[m] Antibodies: Total anti-BMN 111 (TAb), TAb cross-reacting with endogenous natriuretic peptides, and neutralizing antibody (NAb) samples (serum) will be drawn pre-dose at each time point listed on the SOE. TAb cross-reacting with endogenous natriuretic peptides and NAb testing will be performed only on baseline and TAb positive samples from subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg. Drug-specific IgE will be drawn pre-dose on Day 1 for subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg to stay within the limits of permitted blood volume collections in infants. Total immunoglobulin E (IgE) and drug-specific IgE will be drawn in the event of Grade 3 hypersensitivity adverse event) or at Investigator or Sponsor discretion. If such an event occurs, the drug-specific IgE sample should be drawn at least 8 hours after the event start time or 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 an unscheduled safety visit.

[n] Bone metabolism blood biomarkers will be waived at screening for subjects weighing < 7.0 kg to limit the blood volume on the smallest subjects at this visit. Serum samples for bone metabolism biomarkers will be collected pre-dose on the indicated visits. Bone metabolism blood biomarkers include bone-specific alkaline phosphatase and collagen type X.

[o] Urine biomarkers and urine chemistry (urine creatinine test) should be obtained pre- and post-dose (approximately 2-4 hours after study drug administration) for subjects when possible at the indicated visits. The time of collection will be recorded. Urine biomarkers include cGMP and C-terminal telopeptide of cross-linked collagen type II (CTX-II).

[p] 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. Adverse changes from baseline will trigger further evaluation.

[q] MRI is obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC). Efforts to obtain a satisfactory image can be discontinued after 3 unsuccessful attempts.

[r] If sleep study is uninterpretable, subject may need to repeat assessment. Obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC).

[s] WeeFim is waived for children < 6 months old; CBCL is waived for children < 18 months old.

[t] AP lumbar, lateral lumbar, and AP lower extremities are obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC). AP lower extremities X-ray at the Week 52 visit is waived for subjects who cannot stand upright unsupported. Although X-rays are preferable for consistency across the study population, if there are IRBs or IECs unwilling to allow x-rays in Cohort 3 subjects, contact the MM to discuss alternate non-radiological methods for assessment.

[u] To document the physical and phenotypic findings of achondroplasia with and without treatment with study drug, clinical photography of the full body, face, spine, and extremities will be conducted. This assessment is optional. If the parents/caregivers decline clinical photography, the assessment will be waived for the duration of the study.

[v] The injection site should be rotated as described in the BMN-111 Injection Guide. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic. If interruption of study drug injection occurs, the remainder of the assigned dose should be

administered immediately (and no later than within 5 minutes) in a different location. The same syringe should be used and newly reconstituted investigational drug should be used to draw the remainder of the dose.

[w] 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.

[x] All medications (prescription, over-the-counter, herbal, topical) and nutritional supplements taken 30 days prior to screening and throughout the study should be documented.

[y] During the call study staff will ask the caregiver about correct administration procedures, record adverse events (AEs), record concomitant medications, and answer questions.

[z] The 4-week safety follow up visit will be waived for subjects who enter another BMN 111 study or registry within the 4-week period following last dose of study drug.

Table 9.1.2: Schedule of Events Observational Period for Cohort 3 (infants between birth and < 3 months old)

Assessments	Screening[a]	Day 1[a] (Month 0)	3 Months (± 10 days)
Medical history, including growth history and ACH related history	X		
Concomitant medications	X	X	X
Physical examination[b]	X		
Vital signs[c]	X	X	X
Anthropometric measurements[d]		X	X
Vitamin D, 25-hydroxy[e]	X		X
Alkaline phosphatase[e]	X		X
Bone metabolism blood biomarkers	X		X
Bone metabolism urine biomarkers	X		X
Genomic biomarkers (optional)[f]		X	
Weight		X	X
Body mass index (calculated)		X	X
Clinical outcome assessment: Bayley-III[g]		X	
Clinical outcome assessment: ITQOL[g]		X	
Capture all procedures in the Schedule of Events		X	X
Adverse events[h]	X	X	X

[a] Screening and Day 1 (Month 0) assessments may be performed on the same calendar day at the discretion of the investigator. If Screening and Day 1 (Month 0) are done on the same day, vital signs are taken only once. Please refer to eCRF Completion Instructions.

[b] A complete physical examination will be performed at Screening. Complete physical exam includes 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.

[c] Vital signs will be measured with appropriate blood pressure cuffs for achondroplasia children following detailed instructions in Study Reference Manual. At screening, blood pressure should be taken with subject in a supine position, after the subject has been resting for at least 5 minutes. At all other visits, blood pressure should be taken one time after at least 5 minutes of rest, with subject in a supine position. Heart rate should be taken at each time point that blood pressure is measured. Left brachial arm should be the first method of assessment considered, and the same site should be used for blood pressure measurement in each subject throughout the study. The method and site of blood pressure measurement will be recorded and should be utilized consistently throughout the remainder of the study.

[d] Growth parameters (anthropometric measurements) may include but are not limited to height, standing height, sitting or supine height, weight, upper and lower arm and leg length, and arm span. Body proportion measurements may include but are not limited to upper:lower body segment ratio, upper arm:forearm length ratio, upper leg:lower leg length ratio, and arm span:standing height ratio. Refer to the Anthropometric Measurement Guidelines for specific instructions regarding the collection of growth measurements. All age-appropriate physical measurements will be collected at approximately the same time each visit (± 2 hours) by a trained study staff member; every effort will be made to have the measurements collected by the same study staff member, if possible, throughout the study. Each measurement will be taken in triplicate (excluding weight, taken once).

[e] Vitamin D (25-hydroxy) and alkaline phosphatase will be measured during Screening and at the 3-month visit.

[f] If sample is not collected at Day 1, it may be drawn at any time during the study. The sample will be used for exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signaling.

[g] Bayley-III is waived for subjects < 1 month old; ITQOL is waived for subjects < 2 months old.

[h] AEs will be collected at screening. For subjects enrolled in Cohort 3 (0 to < 6 months old), the collection period for all AEs begins after informed consent is obtained.

9.1.1 Dose Adjustments

Analysis of available PK data from studies 111-101 and 111-202 indicated that differences in subject body weight did not directly translate to differences in total body clearance of BMN 111. The same weight-based dose in the pediatric population of Study 111-202 (5-12 years old) yielded lower exposure (C_{max} and AUC) than that characterized in the adult population of Study 111-101. Therefore, the same weight-based dose in the young pediatric population in this study may yield exposure less than the target exposure range characterized to be safe and effective in Study 111-202 at the 15-µg/kg dose. Since this is the first experience with BMN 111 in this young pediatric population, it is also possible the exposure at 15 µg/kg could be greater than the target exposure range, and dose adjustment may be warranted. Thus, an option for adjustment of the weight-based dose is provided to ensure that the appropriate target exposure for safety and efficacy is reached for the young subjects in this study.

The need for dose adjustment will be evaluated as follows: three sentinel subjects in Cohort 1 will receive an initial dose of 15 µg/kg. After all three sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety and PK data (at minimum). If the criteria for dose adjustment are met, the three sentinel subjects will be started on the new adjusted dose at their next scheduled visit, and vital signs will be obtained for at least 4 hours post-dose.

The remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. After the third sentinel subject reaches Week 12 post dose adjustment, a DMC review will occur to evaluate all safety and PK data and, upon endorsement, the three sentinel subjects from the next younger cohort will be enrolled starting at the new adjusted dose. The three sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥ 24 to < 60 months.

Criteria for Dose Adjustment

The criteria for dose adjustment are based on obtaining equivalent exposure characterized to be safe and effective with the 15-µg/kg dose in Study 111-202 in each of the age cohorts evaluated in this study. BMN 111 dose may be adjusted if the mean observed $AUC_{0\text{-}120}$ from

sentinel subjects is less than the 25th percentile for $AUC_{0\text{-}120}$ in Cohort 3 (15 µg/kg) of Study 111-202 or greater than the 75th percentile in Cohort 3 of Study 111-202. If these criteria are met, an allometric scaling coefficient, α, for BMN 111 clearance by subject body weight will be determined using a population PK modelling approach and available data from this study and Studies 111-202 and 111-101. The recommended adjusted dose will be determined using the following expression:

$$Dose_{ch} = Dose_{ref}\left(\frac{WT_{ch}}{WT_{ref}}\right)^{\alpha}$$

where WT_{ref} and $Dose_{ref}$ are the typical (i.e., median) subject body weight and total dose, respectively, at the 15 µg/kg dose level in Cohort 3 of Study 111-202, and WT_{ch} is the anticipated median weight in the age cohort being studied. As such, the recommended adjusted dose will target the median $AUC_{0\text{-}120}$ observed at the 15 µg/kg dose level of Study 111-202. The recommended adjusted dose, $Dose_{ch}$, will be normalized by WT_{ch}, to provide the recommended adjusted weight-based dose. The following rules will be used for dose adjustment:

- A maximum of a 2-fold increase in dose/kg will be permitted between dose adjustments regardless of exposure.
- The total dose will not exceed the highest total dose administered in Study 111-202.

9.1.2 Stopping Criteria

Individual Subject Stopping Criteria

For individual subjects treated with BMN 111, DMC will be informed if any of the following individual subject stopping criteria should occur. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the individual subject will be considered.

- Any treatment-emergent adverse event (AE) assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (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
- Clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec

- Clinically significant new or worsening signs of cervicomedullary compression as determined by the Investigator and in consultation with Sponsor medical monitor and neurosurgical specialist (if needed)
- Adverse findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as determined by the Investigator and in consultation with Sponsor Medical Monitor and orthopedic specialist (if needed)

If the subject meets any stopping criterion, 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
- Permanent treatment discontinuation (with an option of ongoing assessment in the study)

Cohort Stopping Criteria

For each cohort, a DMC review will be conducted if any of the following cohort stopping criteria occur in subjects treated with BMN 111. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the cohort(s) will be considered and the impact on all other age cohorts will be assessed.

- Any treatment-emergent AE assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have a treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any two subjects cohort have a Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Any two subjects have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec
- Any two subjects have adverse 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)

9.2 Discussion of Study Design, Including Choice of Control Group

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are age 0 to < 60 months. Identification of efficacy at this age range is congruent with mechanism of action of BMN 111, because BMN 111 is expected to act at open epiphyseal growth plates. Therefore, to have a potential therapeutic benefit for subjects with ACH, treatment is expected to be required prior to epiphyseal growth plate closure.

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

9.3 Selection of Study Population

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

Additional criteria for participation in the study are provided in Sections 9.3.1 and 9.3.2.

9.3.1 Inclusion Criteria

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

1. Diagnosis of ACH, confirmed by genetic testing. If subjects had previous genetic testing, subjects must have a lab report from a certified laboratory with the study specific mutation documented.
2. Age 0 to < 60 months, at study entry (Day 1)
3. Cohort 1 and 2 subjects must have at least a 6-month period of pretreatment growth assessment in Study 111 901 immediately before study entry, and have one documented measurement of height/body length a minimum of 6 months (+/- 10 days) prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrollment in Study 111-901 or (2) via enrollment in this Study 111 206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment.
4. Parent(s) or guardian(s) (and the subjects themselves, if required by local regulations or ethics committee) 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
5. Willing and able to perform all study procedures as physically possible

6. Parent(s) or caregiver(s) are willing to administer daily injections to the subjects and complete the required training

9.3.2 Exclusion Criteria

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

1. Have hypochondroplasia or short-stature condition other than achondroplasia (e.g., trisomy 21, pseudoachondroplasia, etc.)
2. Subject weighs < 5.0 kg (Cohort 1 and 2) or < 4.0 kg (Cohort 3)
3. Have any of the following:
    - Hypothyroidism or hyperthyroidism
    - Insulin-requiring diabetes mellitus
    - Autoimmune inflammatory disease (including celiac disease, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, etc.)
    - Inflammatory bowel disease
    - Autonomic neuropathy
4. Have a history of any of the following:
    - Renal insufficiency defined as serum creatinine > 2 mg/dL
    - Chronic anemia or Hgb < 10.0 g/dL (based on screening clinical laboratory testing)
    - Baseline systolic blood pressure (BP) below age and gender specified normal range or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms e.g., dizziness, fainting) or recurrent symptomatic orthostatic hypotension
    - Cardiac or vascular disease, including the following
        - Cardiac dysfunction (abnormal echocardiogram determined to be clinically significant by PI and medical monitor) at Screening Visit
        - Hypertrophic cardiomyopathy
        - Pulmonary hypertension
        - Congenital heart disease with ongoing cardiac dysfunction
        - Cerebrovascular disease
        - Aortic insufficiency or other clinically significant valvular dysfunction
        - Clinically significant atrial or ventricular arrhythmias
5. Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening ECG
6. Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator and informed by the following assessments:

- Physical exam (e.g., neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins)
- Polysomnography (e.g., severe central sleep apnea)
- MRI indicating presence of severe CMC or spinal cord damage

7. Have an unstable medical condition likely to require surgical intervention in the next 6 months, or planned spine or long-bone surgery (i.e., surgery involving significant disruption of bone cortex) during the study period
8. Have documented uncorrected Vitamin D deficiency: 25(OH)D $\leq$ 15 ng/mL (37.5 nmol/L)
9. Require any other investigational product prior to completion of the study period
10. Have received another investigational product or investigational medical device within 30 days prior to the Screening visit
11. Have used any other investigational product or investigational medical device for the treatment of achondroplasia or short stature at any time
12. Require current chronic therapy with antihypertensive medication or any medication that, in the investigator's judgment, may compromise the safety or ability of the subject to participate in this clinical study (Table 9.3.5.1)
13. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (> 3 months) at any time
14. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the 12 months prior to screening
15. Have ever had cervicomedullary decompression surgery (Cohorts 2 and 3 only), spine or long-bone surgery (i.e., surgery involving disruption of bone cortex) or have ever had bone-related surgery with chronic complications
    NOTE: Subjects with prior cervicomedullary decompression may be allowed into Cohort 1 only after discussion and agreement with Medical Monitor.
16. Have ever had limb-lengthening surgery or plan to have limb-lengthening surgery during the study period
17. Have had a fracture of the long bones or spine within 6 months prior to screening
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin greater than upper limit of normal (ULN) at screening (except for subjects with a known history of Gilberts or newborns entering screening in Cohort 3)
19. Have evidence of severe untreated sleep apnea; or have newly initiated sleep apnea treatment (eg, CPAP or sleep apnea-mitigating surgery) in the 2 months prior to screening

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 history of hip surgery or severe hip dysplasia
23. Have a history of clinically significant hip injury in the 30 days prior to screening
24. Have a history of slipped capital femoral epiphysis or avascular necrosis of the femoral head
25. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the Investigator
26. 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
27. Have any concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, for any reason

9.3.3 Inclusion Criteria for Cohort 3 Observation Period

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

1. Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, willing and able to provide written assent (if applicable) after the nature of the study has been explained and prior to performance of any research-related procedure.
2. Birth to ≤ 3 months of age at study entry.
3. Have ACH, documented by genetic testing
4. Are willing and able to perform all study procedures as physically possible

9.3.4 Exclusion Criteria for Cohort 3 Observation Period

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 disorders:
   - Hypothyroidism
   - Insulin-requiring diabetes mellitus

- Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others)
- Inflammatory bowel disease
- Autonomic neuropathy

3. Have an unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression
4. Have a history of any of the following:
   - Renal insufficiency
   - Anemia
5. Have a history of cardiac or vascular disease, including the following:
   - Cardiac dysfunction
   - Hypertrophic cardiomyopathy
   - Congenital heart disease
   - Cerebrovascular disease, aortic insufficiency
   - Clinically significant atrial or ventricular arrhythmias
6. Current treatment 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, drugs known to alter renal function that is expected to continue for the duration of the study
7. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable) in the previous 3 months
8. Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
9. Have used any other investigational product or investigational medical device for the treatment of ACH or short stature
10. Planned or expected bone-related surgery (ie. surgery involving disruption of bone cortex), during the study period.
11. Planned or expected to have limb-lengthening surgery during the study period.
12. Have any condition that, in the view of the Investigator, places the subject at high risk of poor compliance with the visit schedule or of not completing the study.
13. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation

9.3.5 Current Chronic Therapy with Restricted Medications

Table 9.3.5.1 lists the medications that are restricted in Study 111-206.

Table 9.3.5.1: Current Chronic Therapy with Restricted Medications

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

9.3.6 Removal of Subjects from Treatment or Assessment

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

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

1. Subject experiences a serious or intolerable AE due to BMN 111 as determined by the subject, investigator, or sponsor
2. Subject requires medication or medical procedure prohibited by the protocol
3. Subject does not adhere to study requirements specified in the protocol
4. Subject is lost to follow-up

If a subject fails to return for scheduled visits, a 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 contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as HIPAA in the US, from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

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

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

BioMarin reserves the right to discontinue the study at any time. Premature termination of the study may occur because of regulatory authority decision, a change in the opinion of the IRB/IEC/REB, clinical or safety reasons, or at the discretion of the Sponsor. The Sponsor reserves the right to discontinue the development of BMN 111 at any time, or to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance. Any decision to terminate the study will be promptly communicated to Investigators, regulatory authorities, and IRB/IEC/REB. The Investigator is responsible for

communicating any decision to terminate a study to hospital staff involved in the conduct of the study and the participating subjects (and their families).

9.3.7 Subject Identification

Each subject will be assigned a unique subject identifier. This unique identifier will be on all eCRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

9.3.8 Duration of Subject Participation

Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in both treatments groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term. For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

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

Follow-up assessments and procedures should be performed as outlined in the Study 111-206 Schedule of Events (Table 9.1.1 and Table 9.1.2).

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

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

9.4 Treatments

9.4.1 Treatments Administered

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

Sentinel subjects will receive BMN 111 at a daily dose of 15 µg/kg (subject to adjustment per protocol). Subjects will be randomized to BMN 111 at a daily dose of 15 µg/kg (subject

to adjustment per protocol) or placebo for the duration of the study. The normal dosing schedule is a single daily subcutaneous injection given 7 days a week.

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

9.4.1.1 Study Drug Administration

During the study, BMN 111 or placebo will be administered as a single 15 µg/kg SC injection given daily at approximately the same time each day whenever possible. Determination of appropriate injection sites will be left to the discretion of the investigator. The same injection site should not be used 2 days in a row, and sites should be rotated. Study drug should be administered at age-appropriate locations (upper thigh, upper back of arm, abdomen or buttocks). Doses may be administered in any of the common SC areas (upper arm, thigh, abdomen, buttocks). Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic. Instructions for home administration of BMN 111 or placebo for subjects who qualify for parent/caregiver administration are provided in the Study Drug Injection Guide and Injection media.

9.4.2 Identity of BMN 111

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

PGQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC

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

9.4.2.1 Product Characteristics and Labeling

The clinical drug product will be supplied in sterile, single-dose, Type I glass vials with coated stopper and flip-off aluminum cap. BMN 111 drug product is supplied as a 0.8-mg or

2-mg lyophilized, preservative-free, white-to-yellow powder for reconstitution with either a sterile diluent or sterile water for injection. The reconstituted solution is colorless to yellow and contains 0.8 mg/mL to 2 mg/mL of BMN 111, as well as citric acid, sodium citrate, trehalose, mannitol, methionine, polysorbate 80, and sterile water for injection. The target pH of the reconstituted solution is 5.5. Sterile water for injection will be commercially sourced and sterile diluent solution containing all of the above excipients will be supplied for reconstitution. All reconstitution and dose preparation steps will be performed as indicated in the BMN 111 Injection Guide and Injection video.

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

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

9.4.3 Storage

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

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

9.4.4 Directions for Administration

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

The injection will be administered as a daily dose of BMN 111 15 µg/kg or placebo given as a single subcutaneous injection. The dose should be given at approximately the same time every day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic. Subjects should have adequate food

intake prior to dosing. All subjects should have been well hydrated and fed in the hour prior to administration of BMN 111 or placebo.

Caregivers will administer BMN 111 or placebo at home once approved by the investigator and adequate training is demonstrated. Instructions on how to complete and document the training can be found in the Study Reference Manual.

A caregiver will be eligible to administer BMN 111 or placebo if he or she meets all of the following criteria:

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

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

The caregiver will be provided with a study diary and will be asked to record daily dosing information, changes in health status, medications and injection sites used, date and time of the injection, and injection site reactions, if any.

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

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 ratio, i.e., injection with placebo:15 µg/kg of BMN 111, using IXRS. An independent third-party vendor will develop the randomization schedule so that BioMarin and site personnel are blinded to treatment assignments. NOTE: In Japan, subjects are randomized separately within each cohort.

9.4.6 Selection of Dose and Dosing Schedule Used in the Study

Study 111-202, the second clinical trial in humans and the first in children with ACH, is an ongoing Phase 2, open-label, sequential-cohort, dose-escalation study that assesses daily SC BMN 111 in pediatric subjects with ACH aged 5-14 years with doses ranging from 2.5 µg/kg to 30 µg/kg.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at the doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated. The most common AEs across all cohorts were injection site reactions, asymptomatic hypotension, headache, and nasopharyngitis. Based on previous experience of the ongoing Phase 2 clinical trial, including the 24-month data cut at 15 µg/kg, injection site reactions have been identified as risks associated with BMN 111 injections. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

Analysis of efficacy data from the 6-month initial phase of Study 111-202 showed that subjects treated with BMN 111 for 6 months at doses ranging from 2.5 to 15 µg/kg daily had a dose-dependent improvement in AGV, with ~50% improvement in AGV seen at the 15 µg/kg dose. The data from Cohort 4 (30 µg/kg) show an apparent greater than dose-proportional increase in BMN 111 plasma exposure (C_{max} and AUC_{0-t}), 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).

Efficacy/toxicity studies have been conducted in neonatal and very young animals (7-day postpartum mouse and rat) in both a disease (TD mouse) and non-disease (rat) model. Given that this is the first study in infants and young children, an age-based cohort study design is used to assess safety and PK in young children (Cohort 1, ≥ 24 to < 60 months) prior to dosing toddlers (Cohort 2, ≥ 6 to < 24 months) and infants (Cohort 3, 0 to < 6 months). PK will be monitored and evaluated; Day 1 PK data from the sentinel subjects will inform dose selection modification for the sentinel subjects and for the rest of the cohort to target the observed exposure of the 15-µg/kg dose group in Study 111-202. Safety, efficacy and PK data from Study 111-202, a Phase 2 study in children with ACH, where a dose of 15 µg/kg has been and continues to be studied, are expected to be the most relevant, and translatable to this study (111-206).

9.4.6.1 Selection of Timing of Dose for Each Subject

9.4.7 Blinding

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

The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure. In the event of an

emergency medical situation where subject management would be determined or significantly altered by knowing the treatment assignment, the investigator may be unblinded without prior written approval from the Medical Monitor. Following such an emergency unblinding, the investigator will contact the medical monitor and provide written rationale according to the unscheduled unblinding procedure set forth in the Study Manual.
The Medical Monitor will review the rationale, evaluate whether there are any additional safety considerations that need to be implemented for the subject and/or the study, and determine whether the investigator requires further guidance on unblinding. The Medical Monitor may also communicate with the investigator advice on the care of the subject and define the plan for the subject's future participation in the study.

9.4.8 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 eCRF. The Investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

9.4.9 Treatment Compliance

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

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

9.5 Investigational Product Accountability (BMN 111 or Placebo)

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

9.5.1 Return and Disposition of Clinical Supplies

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

Unused BMN 111 or placebo may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for destruction. The study monitor must account for all BMN 111 or placebo kits/vials in a formal reconciliation process prior to destruction. The site must document all BMN 111 or placebo destroyed on site, and documentation must be provided to BioMarin and retained in the investigator study files. If a site is unable to destroy BMN 111 or placebo appropriately, the site can, upon request, return unused BMN 111 or placebo to the BioMarin contracted facility. The return of all BMN 111 or placebo kits/vials must also be documented and accounted for per instructions provided by BioMarin.

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

9.6 Dietary or Other Protocol Restrictions

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

Subjects should have adequate food intake prior to dosing. All subjects should have been well hydrated and fed in the hour prior to administration of BMN 111 or placebo.

9.7 Demographic Data and Medical History

Demographic data and a detailed medical history will be obtained at Screening. This 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; and evaluation for knee, thigh, hip or groin pain, or change in gait/activity.

9.8 Biological Parental Standing Height

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

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. Other body systems may be examined. Screening results will be the baseline values and clinically significant changes from baseline will be recorded as an AE or SAE and study drug related or unrelated when appropriate based on the investigator's clinical judgment.

9.10 Echocardiogram

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

9.11 Efficacy and Safety Variables

9.11.1 Efficacy and Safety Measurements Assessed

The Schedule of Events (Table 9.1.1 and Table 9.1.2) describes the timing of required evaluations.

9.11.2 Primary Efficacy Variables

The primary efficacy endpoint is change from baseline in length/height Z-score.

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

9.11.3 Secondary Efficacy Variables

The secondary efficacy endpoints include change from baseline in AGV (annualized to cm/yr), biomarker samples to evaluate the effect of BMN 111 on bone metabolism, and BMN 111 pharmacodynamic biomarkers.

Weight will be measured at Screening and at study visits as indicated on the Schedule of Events (Table 9.1.1 and Table 9.1.2).

Biomarkers may include but are not limited to assessment of changes in bone and collagen metabolism (serum bone-specific alkaline phosphatase, serum collagen type X, and urine C-terminal telopeptide of collagen type II [CTX-II]) and BMN 111 bioactivity (plasma and urine cGMP). BioMarin or designee will perform analysis, and samples may also be used for assay development.

Samples for blood and/or urine biomarkers will be collected at the time points presented in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Refer to the Study Laboratory Manual for instructions regarding obtaining and shipping samples. The sample type will also be included in the Study Laboratory Manual.

9.11.4 Exploratory Efficacy Variables

9.11.4.1 Body Proportion Ratios of the Extremities

Change from baseline in body proportion ratios of the extremities will be evaluated using anthropometric measurements and measurement ratios. Refer to the Anthropometric Measurement Guidelines for specific instructions regarding the collection of growth measurements. All age-appropriate physical measurements will be collected at approximately the same time each visit (±2 hours around the time when the first measurement assessment was taken at Screening) by a trained study staff member; every effort will be made to have the measurements collected by the same study staff member, if possible, throughout the study. Each measurement will be taken in triplicate (excluding weight, taken once).

Anthropometric measurement can be conducted either pre-dose or post-dose. Measurements may include but are not limited to length, standing height (if able to stand unsupported), crown-to-rump length, head circumference, upper and lower arm and leg, and arm span. Measurements not taken in the midsagittal plane should be taken on the right side of the body if possible and should always be taken on the same side of the body throughout the study

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

9.11.4.2 Imaging Assessment Procedures (per Schedule of Events)

Imaging assessment procedures for all visits must be performed using the same instruments. Imaging assessments can be conducted either pre-dose or post-dose.

- Bilateral lower extremity x-rays, anterior-posterior (AP) view, to assess growth plate morphology.
- Hip imaging via pelvis x-ray to identify hip pathology
- Lumbar spine x-rays to measure changes from baseline in bone morphology and pathology.
- MRI to evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions.
- DXA (BMD and BMC) of whole body [less head], spine, and forearm (including ultra-distal, mid-distal, and one third radius regions of interest) to assess bone mineral density (BMD) and bone mineral content (BMC).

Although X-rays are preferable for consistency across the study population, if there are IRBs or IECs unwilling to allow x-rays in Cohort 3 subjects, contact the medical monitor to discuss alternate non-radiological methods for assessment.

Additional imaging may be conducted should there be any issues or concerns with the subject's imaging assessments. Imaging assessments will be collected and interpreted by a central reader. If clinically significant abnormalities are noted, the investigator or designee is required to assess whether it is appropriate to report an AE and if the subject should continue in the study. Refer to the vendor Imaging Guidelines for detailed imaging assessment requirements and procedures.

9.11.4.3 Exploratory Biomarker Research Sample Analyses

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

For each portion of the blood and urine samples reserved for protocol-specified analyses, there may be multiple sample aliquots. Once samples have been successfully analyzed during the study, unused sample portions may be used during the study for assay development or other purposes stated in this section. No exploratory genomic research will be conducted without consent from the subject and his/her legally authorized representative (parent or legal guardian).

9.11.4.4 Genomic Biomarker Analysis

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

9.11.4.5 Sleep Study

Given that sleep apnea is a finding in children with ACH (Waters, 1993) and has implications on functional and health outcomes, a sleep study will be performed in a limited number of qualified sleep centers. A sleep-testing device will be used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea will include, but may not be limited to, the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index).

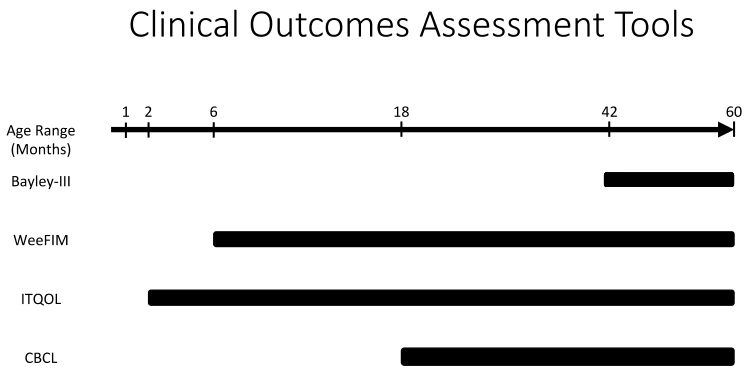
9.11.4.6 Clinical Photography

To document the physical and phenotypic findings of achondroplasia with and without treatment with study drug, clinical photography of the full body, face, spine, and extremities will be conducted. This assessment is optional. If the parents/caregivers decline clinical photography, the assessment will be waived for the duration of the study.

9.11.4.7 Clinical Outcome Assessments

Clinical outcome assessments will be administered to assess the health-related quality of life of study subjects. ADL questionnaires will be performed in study subjects to assess functional performance. Clinical outcome assessments will be performed at the time points indicated in the Schedules of Events (Table 9.1.1 and Table 9.1.2). The age ranges for clinical outcome assessment tools are shown in Figure 9.11.4.7.1.

Figure 9.11.4.7.1: Clinical Outcomes Assessment Tools



9.11.4.7.1 Bayley-III

The Bayley-III is a performance-based outcome assessment for use in children from 1 to 42 months. It is individually administered by the trained clinician to the subject/child. The time required varies from 15-60 minutes depending on the child's developmental level and cooperation.

Scales include Cognitive subscale, Receptive and Expressive subscales, and Gross and Fine Motor subscales. The two language scales make up a composite Language Scale score and the Gross and Fine Motor subscales yield a composite Motor Scale score.

The scales have clinical and research utility as a diagnostic assessment for young children with varied disorders and disabilities, and reflect current professional standards for early childhood assessment (Bayley, 2006).

In addition to its use for subjects ranging from 1 to 42 months old, the Bayley-III assessment will be administered to those entering the study between 42 and 60 months old (Figure 9.11.4.7.1) and for the remainder of the duration of this study, as this assessment can capture ongoing developmental issues associated with Achondroplasia. Bayley-III is waived for subjects <1 month old.

9.11.4.7.2 Activity of Daily Living and Functional Independence Measure (Wee-FIM)

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

The Wee-FIM instrument has been used in previous research in children with ACH, and has identified ongoing limitations in functional performance across these domains extending beyond the age of 7 years (Ireland, 2011). Because the WeeFIM considers the child's performance from a caregiver's perspective (Ireland, 2012), this tool in turn gives an indication of "burden of care" for families and caregivers of children with ACH. WeeFIM is waived for children < 6 months old.

9.11.4.7.3 ITQOL

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

9.11.4.7.4 Child Behavior Checklist

The Child Behavior Checklist (CBCL) is for use in children from 1.5-5 years old, and will be administered for those entering the study at less than 5 years old and for the remainder of the duration of the study. The CBCL comprises 99 questions addressing symptoms related to mood, behavior issues, and sleep disturbance. It is completed by the parent or primary caregiver.

The form requires approximately 15 minutes to complete. The checklist yields scores in the following areas: reactivity, anxiety, depression, somatic complaints, withdrawal, sleep problems, attention problems, and aggressive behavior. CBCL is waived for children < 18 months old.

9.11.5 Pharmacokinetics Variables

PK plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes. In the event of interruption of study drug administration for a sentinel patient on Day 1 when PK samples are scheduled, the collection of PK samples should be delayed until the subsequent day and only performed after successful administration of study drug has been completed in a single injection.

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

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

9.11.6 Safety Variables

Safety will be evaluated by the incidence of AEs, SAEs, and clinically significant changes in vital signs, physical examination, ECG, imaging, and laboratory test results (urinalysis, chemistry, hematology). Additionally, imaging, hip monitoring, biomarker, immunogenicity, cortisol and prolactin levels, and physical measurement data will be utilized for safety-related reviews and analysis.

9.11.6.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject receives study drug. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10.2.1. Assessments of AEs will occur at the time points shown in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Additionally, contact by a study staff member to the caregiver will be required every week for 6 months, and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

9.11.6.2 Procedures During the Study

All procedures/intervention/surgery will be recorded after informed consent is obtained and after the first administration of study drug, until end of study.

9.11.6.3 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1 and Table 9.1.2. The scheduled clinical laboratory tests are listed in Table 9.11.6.3.1. Refer to the Study Reference 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.

The investigator should assess all abnormal clinical results and include a comment on whether or not the result is clinically significant. Each clinically significant laboratory result should be recorded as an adverse event.

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 eCRF.

Table 9.11.6.3.1: 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
Glucose		
Bicarbonate		Urine Chemistry Urine creatinine Urine sodium Urine potassium
LDH Phosphorus		
Total protein 25-hydroxy Vitamin D		
Creatinine Thyroid function (TSH, FT4; if either TSH and FT4 are abnormal then T3 may be measured in addition)		

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

9.11.6.4 Other Laboratory Assessments

Subjects will be asked to provide blood and urine at the times indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Blood volume for testing has been reduced to the minimum necessary for adequate evaluation of efficacy and safety of BMN 111.

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

Salivary cortisol and serum prolactin will be collected at the times indicated in the Schedule of Events (Table 9.1.1).

Scheduled biomarker and anti-BMN 111 antibody tests are listed in Table 9.11.6.4.1.

Table 9.11.6.4.1: Biomarkers and Anti-BMN 111 Antibodies

Blood Special Chemistry	Urine Biomarkers
Exploratory bone metabolism biomarkers: bone-specific alkaline phosphatase and collagen type X	Exploratory bone metabolism urine biomarkers: C-terminal telopeptide of collagen type II
Genomic biomarkers	BMN 111 pharmacodynamics biomarkers (cGMP)
Anti-BMN 111 antibodies	
BMN 111 pharmacodynamics biomarker (cGMP)	BMN 111 pharmacodynamics biomarker (cGMP)

cGMP, cyclic guanosine monophosphate

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

Vital signs assessed pre-dose will include seated or supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). All treatment visits have pre-dose vital sign assessments. Post-dose measurements include heart rate and BP. For all dosing visits, assessment frequency is detailed in Table 9.11.6.5.1 (Schedule of Events, Table 9.1.1 and Table 9.1.2).

At Screening, after at least 5 minutes of rest, subject's BP is taken in sitting or supine position. Vital sign measurements should be repeated and documented 3 times, with at least 5-minute intervals between assessments. Left brachial arm should be the first method of assessment considered, and the same site should be used for blood pressure measurement in each subject throughout the study. The method and site of blood pressure measurement will be recorded and should be utilized consistently throughout the remainder of the study.

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

If a subject has signs 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 signs (if present) resolve. If the hypotension resolves within the first hour and returns to the normal range, additional BP monitoring as described above is not required. Detailed guidance for blood pressure measurements is provided in the Blood Pressure Instrument and Technique Guidelines.

Table 9.11.6.5.1: Vital Sign Assessment Frequency

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

1. Vital sign measurements are taken once per time point, preferably in a sitting or supine position, after at least 5 minutes of rest.
2. Heart rate, blood pressure, and respiratory rate should be taken and recorded at each indicated time point.
3. When blood samples and vital sign assessments are scheduled at the same time or within the same time window, vital signs should be measured before blood samples are drawn.
4. If a vital sign measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and wait several minutes before measuring vital signs.
5. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
6. If a subject has a hypotensive event, or signs potentially consistent with hypotension, or a decrease of 20 mm Hg systolic BP or more from baseline (defined by pre-dose vitals collected that day), vital signs should be measured and recorded approximately every 15 minutes (± 5 minutes) for the first hour and every 30 minutes (± 5 minutes) thereafter until the BP returns to baseline (or within the normal range for this subject as defined by PI) and signs (if present) resolve.
7. If the decision is made to adjust the dose, vital signs will be obtained for at least 4 hr following the first dose at the adjusted dose level, similar to the Day 3, 8 schedule.
8. If a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1,2 schedule.

9.11.6.6 Mitigating the Risk of Potential Hypotension

Study personnel and caregivers should be made aware of the potential risk of hypotension with BMN 111 administration. Subjects must be well hydrated and at a minimum be fed

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

Caregivers should be trained to observe and recognize the signs of dehydration (e.g. from fever, vomiting, diarrhea, etc.) and contact the investigator prior to BMN 111 or placebo administration if dehydration is suspected. Site personnel and caregivers should be trained to identify the signs 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 10.3.1.4.

9.11.6.7 Electrocardiography

A standard 12-lead ECG will include heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. The time of collection will be recorded. ECGs should be performed in triplicate with the subject supine at the visits indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). ECGs will be performed post-dose on study day visits at which a dose is given; in addition, on Day 1, ECGs will be performed pre-dose. On days when PK samples are being drawn, ECGs should be performed within a 5-minute window prior to 30-minute PK assessment. 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.

9.11.6.8 Hip Clinical Assessment

The hip clinical assessment should be completed by an appropriately qualified physical therapist or a physician (MD) i.e., the investigator or the sub-investigator at the time points indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Medical history will be obtained to evaluate for hip, thigh, or knee pain, or change in gait. The physical exam (including observation of gait when possible) identifies and evaluates any changes in hip function or pain with assessment of active and passive range of motion. Changes from baseline may trigger further evaluation based on the investigator's clinical assessment, which may include hip imaging and/or orthopedic consultation. If findings on clinical hip exam are determined to be clinically significant by the investigator and in consultation with Sponsor's Medical Monitor and orthopedic specialist (if needed), the DMC will be notified of AEs resulting from clinically significant abnormal hip monitoring assessments. DMC may

provide recommendations as to if/when BMN 111 or placebo treatment should be temporarily or permanently discontinued.

9.11.6.9 Pediatric Blood Volume

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

To minimize blood collection volumes, assay technologies were chosen that are capable of sensitively detecting analytes using the lowest possible volume of blood for analysis. Additionally, assays capable of detecting analytes in urine rather than blood have been selected where possible.

9.11.6.10 Anti- BMN 111 Immunogenicity Assessments and IgE Testing

Subjects randomized to receive BMN 111 or placebo will undergo immunogenicity testing. Blood (serum) samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 9.1.1), and testing performed using validated assays. Neutralizing antibody (NAb) testing will be performed on Baseline and TAb positive samples drawn from subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg.

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

- Anti- BMN 111 total antibody (TAb)
- Anti-BMN 111 antibody cross-reactive with endogenous CNP, ANP, and BNP (TAb)
- Anti- BMN 111 NAb

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

9.11.6.11 HPA Axis Assessments

To address potential effects of BMN 111 on activation of the hypothalamic pituitary adrenal (HPA) axis, assessment of salivary cortisol and serum Prolactin levels will be analyzed at the time points indicated in the Schedule of Events (Table 9.1.1). Both tests will be done at Baseline, Week 26, and Week 52.

9.11.6.12 Ad Hoc Safety Assessments

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

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

- Drug-specific IgE
- Total IgE
- Serum tryptase

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

A localized injection site reaction is defined as skin signs or signs 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).

9.11.6.13 Unscheduled Safety Visits

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

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

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

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

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 1 or more of the following criteria:

- Is fatal
- Is life threatening

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

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

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

10.1.3 Events of Special Interest (EOSI)

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

- Fracture
- Slipped Capital Femoral Epiphysis (SCFE)
- Avascular necrosis or Osteonecrosis

10.2 Methods and Timing for Capturing and Assessing Safety Parameters

10.2.1 Adverse Event Reporting Period

For subjects enrolled in Cohort 1 (≥ 24 to <60 months old) and Cohort 2 (≥6 to <24 months old), the study AE reporting period is as follows: after informed consent but prior to initiation of study treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, all non-serious AEs and SAEs reporting period begins and continues until 4 weeks following either the last administration of study drug or the early termination visit, whichever is longer (refer to Section 12.1.11). The criteria for determining, and the reporting of, SAEs is provided in Section 10.1.2. For subjects enrolled in Cohort 3 (0 to< 6 months old), the collection period for all AEs begins after informed consent is obtained.

10.2.2 Eliciting Adverse Events

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

10.2.3 Assessment of Seriousness, Severity, and Causality

The Investigator or qualified designee responsible for the care of the subject 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 (e.g., MD/DO, physician's assistant, nurse practitioner, or DDS).

10.2.3.1 Seriousness

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

10.2.3.2 Severity

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

The Investigator or qualified designee will determine the severity of each AE and SAE, and EOSI 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 activities of daily living (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 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 eCRF. 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[a]	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 not be explained by factors or causes other than exposure to the IP **OR** • The administration of IP and the occurrence of the AE are reasonably related in time AND • The AE is more likely explained by exposure to the IP than by other factors or causes.

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against

cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.3 Procedures for Recording Adverse Events

10.3.1 Recording Adverse Events on a 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 (e.g., 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 sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, then this diagnosis should be entered on the AE form, replacing the original entries where appropriate.

10.3.1.2 Adverse Events Occurring Secondary to Other Events

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

10.3.1.3 Persistent or Recurrent Adverse Events

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

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

10.3.1.4 Hypotension

If an asymptomatic drop in blood pressure meets the protocol definition of AE per clinical judgment of the reporter, report the event as “blood pressure decreased.” If the drop in blood

pressure is associated with signs or symptoms, complete the symptomatic hypotension eCRF and use the following guidance to report the corresponding AE eCRF: If a unifying diagnosis is available to explain the event of hypotension, report the diagnosis as an AE and capture signs and symptoms on the symptomatic hypotension eCRF page. If no other unifying diagnosis is available, report "hypotension" as the event and capture signs and symptoms on the symptomatic hypotension eCRF page.

10.3.1.5 Injection Site Reactions

If an injection site reaction is associated with a single sign or symptom, report the event on AE eCRF page (e.g., redness at injection site, AE is injection site redness). If the injection site reaction is associated with multiple signs or symptoms, report injection site reaction as the adverse event on the AE page, and individual signs and symptoms will be reported on the ISR eCRF page (e.g., if the subject experiences redness and induration, report "Injection site reaction" on the AE page, and in the corresponding Injection eCRF page, report erythema and induration). If the injection site reaction appears after 24 hours, add "delayed" to the term used to describe the event.

10.3.1.6 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 it is not otherwise refuted by a repeat test to confirm the abnormality and **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 abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., 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.

10.3.1.7 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., *more frequent* headaches).

10.3.1.8 General Physical Examination Findings

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

10.3.1.9 Hospitalization, Prolonged Hospitalization, or Surgery

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

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

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

10.3.1.10 Deaths

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

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

10.4 Reporting Requirements

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

10.4.1 Expedited Reporting Requirements

All SAEs and EOSI, if applicable 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 entering the information in the AE eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. Each SAE must also be reported on the appropriate eCRF. Investigators should not wait to collect information that fully documents the event before notifying BPV of an SAE. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit any information requested by BioMarin as soon as it becomes available.

If the electronic data capture (EDC) is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

The reporting period for SAEs begins after informed consent is obtained and continues until 4 weeks following either the last administration of study drug or study discontinuation/termination, 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 Subjects after Adverse Events

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

For some SAEs, the Sponsor may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (eg, hospital discharge summary, consultant report, 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 subject to report, to the Investigator and/or to BPV directly, any subsequent SAEs that the subject's personal physician(s) believes might be related to prior study treatment.

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

10.7 Urgent Safety Measures

The regulations governing clinical trials state that the sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, 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 subjects, the sponsor and the Investigator shall take appropriate urgent safety measures to

protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/EC/REB is notified at the same time."

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

The reporting period for these events which may require the implementation of urgent safety measures is the period from the time of signing of the ICF through the completion of the last study visit or at the Early Termination Visit (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
Phone: PI
Fax: PI
E-mail: drugsafety@bmrn.com

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

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

11 APPROPRIATENESS OF MEASUREMENTS

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

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

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

Bone-related biomarkers and other biochemical markers of the pharmacological activity of BMN 111 in the blood or urine are secondary assessments. Genomic biomarkers are exploratory assessments.

12 STUDY PROCEDURES

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

12.1 Treatment Visit(s)

12.1.1 Screening/Baseline Day -30 to Day -1

- Medical history
- Parental height
- Diagnostic genetic testing to confirm achondroplasia (if needed)
- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Echocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Thyroid function tests
- Vitamin D, 25-hydroxy test
- Salivary cortisol
- Serum prolactin
- Bone metabolism blood biomarkers
- Screening baseline hip assessment with pelvis x-ray
- MRI brain/skull
- Sleep study
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- DXA
- AP and lateral X-rays of spine

- AP X-rays of lower extremities
- Clinical photographs (optional)
- Concomitant medications

12.1.2 Day 1 and Week 13 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Plasma pharmacokinetics and cGMP assessments
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture all procedures
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.3 Days 2 and 3

- Physical examination
- Weight
- Vital signs
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture all procedures
- BMN 111 or placebo administration

- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.4 Day 8 (±1d) and Week 20 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Bone metabolism blood biomarkers
- Capture all procedures
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.5 Week 3 (±7d)

- Physical examination
- Weight
- Vital signs
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture all procedures
- BMN 111 or placebo administration
- BMN 111 or placebo accountability

- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.6 Week 6 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Genomic biomarkers (optional)
- Bone metabolism blood biomarkers
- Capture all procedures
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.7 Week 26 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Salivary cortisol
- Serum prolactin
- Plasma pharmacokinetics and cGMP assessments
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers

- BMN 111 pharmacodynamic biomarkers
- Urine chemistry
- Hip monitoring
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- Capture all procedures
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.8 Week 39 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Plasma pharmacokinetics and cGMP assessments
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture all procedures
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events

- Concomitant medications
- Phone call or home health visit

12.1.9 Week 52 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Thyroid function tests
- Vitamin D, 25-hydroxy test
- Salivary cortisol
- Serum prolactin
- Plasma pharmacokinetics and cGMP assessments
- Anti-BMN 111 immunogenicity
- Genomic biomarkers (optional)
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Hip monitoring
- MRI brain/skull
- Sleep study
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- DXA
- AP and lateral X-rays of spine
- AP X-rays of lower extremities

- Clinical photographs (optional)
- Capture all procedures
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.10 Week 56 Safety Follow-up (+7d)

- Physical examination
- Vital signs
- Electrocardiogram
- Echocardiogram
- Capture all procedures
- Adverse events
- Concomitant medications

12.1.11 Early Termination Visit

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Echocardiogram (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Salivary cortisol
- Serum prolactin
- Anti-BMN 111 immunogenicity
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers

- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Hip monitoring
- MRI brain/skull (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
- Sleep study (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: WeeFIM
- Clinical outcome assessment: ITQOL
- Clinical outcome assessment: CBCL
- DXA
- AP and lateral X-rays of spine (obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination)
- AP X-rays of lower extremities (obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination)
- Clinical photographs (optional)
- Capture all procedures
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications

12.2 Observational Period for Cohort 3 (Infants between birth and <3 months old [0 days to <13 weeks])

12.2.1 Screening Visit

- Medical history, including growth history and ACH-related history
- Concomitant medications
- Physical examination
- Vital signs
- Vitamin D, 25-hydroxy
- Alkaline phosphatase

- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- Adverse events

12.2.2 Day 1 (Month 0)

- Concomitant medications
- Vital signs
- Anthropometric measurements
- Genomic biomarkers (optional)
- Weight
- Body mass index (calculated)
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: ITQOL
- Capture all procedures
- Adverse events

12.2.3 3 Months (± 10 days)

- Concomitant medications
- Vital signs
- Anthropometric measurements
- Vitamin D, 25-hydroxy
- Alkaline phosphatase
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- Weight
- Body mass index (calculated)
- Capture all procedures
- Adverse events

13 DATA QUALITY ASSURANCE

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

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

Sites will enter study data into eCRFs into the study EDC system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS v. 9.4.

14.1.1 Interim Analyses

An interim analysis will be carried out to support NDA/MAA filing. The report will be provided by a third party to assure that the study team, subjects, and investigators have no access to the individual subject treatment allocation.

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

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

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

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

14.2 Safety Analysis

The safety analysis will be performed on safety population as defined in Section 14.7.2 and will be considered descriptive.

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

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment (as assessed by investigator), and severity. All AEs, including SAEs and AEs that lead to permanent discontinuation from the study and from the study treatment, will be listed. Hypersensitivity reactions and

symptomatic hypotension are of interest, and the percentage of subjects who report these AEs will be presented. Hypersensitivity reactions will be defined in the SAP.

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

All other safety measures including laboratory tests, vital signs, ECG, echocardiogram, hip clinical assessment, and concomitant medication data will also be summarized descriptively. Data summaries will be presented by treatment group (when applicable) for each cohort and overall. All safety results will be listed.

14.3 Efficacy Analysis

Efficacy analysis will be performed on the efficacy population as defined in Section 14.7.1. Efficacy endpoints include length/height AGV and length/height standard score (Z-score) at Week 52.

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

$$\text{AGV} = \frac{\text{Length/standing height at Day 2} - \text{Length/standing height at Day 1}}{\text{Interval Length (Days)}} \times 365.25$$

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

- Baseline: [Date of last length/height measurement in study 901 at least 6 months prior to screening visit in study 206, Date of Day 1]
- Week 13: [Date of Day 1, Date of Week 13]
- Week 26: [Date of Day 1, Date of Week 26]
- Week 39: [Date of Day 1, Date of Week 39]
- Week 52 (12-month): [Date of Day 1, Date of Week 52]

The baseline of the AGV is established in the natural history study of Study111-901, based on the standing height measurements in the last 6 months prior to enrollment to Study 111-206. AGV will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum). Results will be summarized by treatment group and cohort.

The measurement of length/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.

Comparisons between treatment groups by cohort on these variables will be carried out where appropriate. Statistical comparisons will be considered descriptive. Additional details regarding efficacy analysis will be provided in the SAP.

14.4 Pharmacokinetic Analyses

Subjects randomized to receive BMN 111 or placebo will undergo pharmacokinetic testing.

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

14.5 Immunogenicity Analysis

Immunogenicity will be summarized as change from baseline as well as by study time point in subjects randomized to receive BMN 111 or placebo. Results will be summarized as incidence and titer for all cohorts. Additionally, immunogenicity may be assessed for correlations with measures of safety, PK, and efficacy.

14.6 Determination of Sample Size

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

14.7 Analysis Populations

14.7.1 Efficacy Population

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

14.7.2 Safety Population

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

15 DATA MONITORING COMMITTEE

In addition to safety and PK 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. After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort will be opened and the 3 sentinel subjects will be enrolled.

The DMC will make recommendations for stopping or continuing the study on an individual subject level and/or on a cohort level per the pre-specified stopping criteria. Based on criteria outlined in the protocol, the DMC may also make endorsements for dose adjustments if needed.

Please see DMC Charter for further details.

16 COSTS, COMPENSATION, AND SUBJECT INJURY

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

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

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

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

eCRFs must be completed using a validated web-based application. Study site personnel will be trained on the application and will enter the clinical data from source documentation. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representative) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If direct source document verification of study data by the site monitor is prohibited by institutional policy or local law, then the Investigator must make available facilities and/or personnel to allow GCP-compliant source verification to occur. Examples of such methods include certified copies of records which have study data visible but sensitive information redacted, or other GCP-compliant means agreed between the Investigator and the Sponsor.

A CRA designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" (SDV). If an error is discovered at any time or a clarification is needed, the CRA, or designee, will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Before a subject's eCRF casebook can be locked, data fields must be source data verified and all queries closed. Refer to the 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 eCRFs 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 sent to each site for retention with other study documents.

18 STUDY MONITORING AND AUDITING

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

Members of BioMarin's GCP Compliance Department or designees may conduct an audit of a clinical site at any time before, during, or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an 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.

19 RETENTION OF RECORDS

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

20 USE OF INFORMATION AND PUBLICATION

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

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572 and/or principles of ICH E6 GCP, the Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes. He or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and/or ICH E6 Sections 2.9 and 4.8 are met, as well as IRB/IEC review and approval requirements in 21 CFR Part 56 and/or ICH E6 GCP Section 2.6.
- 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 and/or ICH E6 GCP Section 4.11.
- 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 are in accordance with 21 CFR 312.62 and/or ICH E6 Section 4.9, and will make those records available for inspection in accordance with 21 CFR 312.68 and/or ICH Section 4.9.7.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH Section 3.0 and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312 and/or ICH E6 R2.

23 SIGNATURE PAGE

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

Protocol Number: 111-206A1

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

Investigator Signature Date

Printed name: _____

Accepted for the Sponsor:

PI

PI

Medical Monitor Signature Date

Printed name: PI MD, PhD

24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the major revisions and administrative changes made to the protocol body (corresponding changes have been applied in the synopsis but are not shown here) in Amendment 1, and relates the changes to the appropriate rationale (see pages 2-5). Text that has been added or inserted is indicated by underlined font, and deleted text is indicated by ~~strikethrough~~ font.

Section No./Title	**Text Revisions**
Rationale #1: **The lower age range of participating subjects who have a ≥ 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry has been revised from ≥ 3 months to ≥ 6 months**	
Section 9.1 Overall Study Design and Plan	Subjects age~~≥ 3~~ ≥ 6 months to < 60 months old who have documented ACH confirmed by genetic testing; at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before study entry; and who meet the study eligibility criteria, will participate. Eligible subjects ranging from 0 months to~~<~~ ≤ 3 months old may enroll directly into 111-206 and have a minimum of 3 months of pre-treatment observation prior to commencing treatment with investigational product, or may enroll in 111-901 for a minimum of 3 months of pretreatment growth assessment immediately before roll-over to 111-206.
Rationale #2: **No two sentinel subjects will be dosed on the same day for any cohort**	
Section 9.1 Overall Study Design and Plan	No two sentinel subjects will be dosed on the same day for any cohort.
Rationale #3: **Echocardiogram will be performed at the Week 56 Safety Follow-up and Early Termination visits**	
Table 9.1.1 Section 12.1.10 Week 56 Safety Follow-up	• Echocardiogram
Section 12.1.11 Early Termination Visit	• Echocardiogram (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
Rationale #4: **Use of residual plasma samples for cGMP PD biomarker assessment in all age groups has been added to procedures**	
Table 9.1.1	~~Pharmacokinetics assessments~~ Plasma pharmacokinetics and cGMP assessments[l]
Table 9.11.6.4.1	**Blood Special Chemistry** / **Urine Biomarkers**

<table>
<tr><th>Section No./Title</th><th>Text Revisions</th></tr>
<tr><td></td><td>
<table>
<tr><td>Exploratory bone metabolism biomarkers: bone-specific alkaline phosphatase and collagen type X</td><td>Exploratory bone metabolism urine biomarkers: C-terminal telopeptide of collagen type II</td></tr>
<tr><td>Genomic biomarkers</td><td>BMN 111 pharmacodynamics biomarkers (cGMP)</td></tr>
<tr><td>Anti-BMN 111 antibodies</td><td></td></tr>
<tr><td>BMN 111 pharmacodynamics biomarker (cGMP)</td><td>BMN 111 pharmacodynamics biomarker (cGMP)</td></tr>
</table>
cGMP, cyclic guanosine monophosphate
</td></tr>
<tr><td>Sections:
12.1.2 Day 1 and Week 13
12.1.7 Week 26
12.1.8 Week 39
12.1.9 week 52</td><td>• ~~Pharmacokinetics~~ Plasma pharmacokinetics and cGMP assessments</td></tr>
<tr><td colspan="2">Rationale #5:
An anti-BMN 111 immunogenicity assessment has been added at Week 3</td></tr>
<tr><td>Table 9.1.1
Section 12.1.5 Week 3</td><td>• Anti-BMN 111 immunogenicity</td></tr>
<tr><td colspan="2">Rationale #6:
Bone metabolism urine biomarkers, BMN 111 pharmacodynamic urine biomarkers, and urine chemistry assessments have been added at Week 39</td></tr>
<tr><td>Table 9.1.1
Section 12.1.8 Week 39</td><td>• Bone metabolism urine biomarkers
• BMN 111 pharmacodynamic urine biomarkers
• Urine chemistry</td></tr>
<tr><td colspan="2">Rationale #7:
The sleep study scheduled at the Week 26 visit has been removed</td></tr>
<tr><td>Table 9.1.1
Section 12.1.7 Week 26</td><td>• ~~Sleep study~~</td></tr>
<tr><td colspan="2">Rationale #8:
DXA scans will no longer include tibia scans</td></tr>
<tr><td>Table 9.1.1
Section 9.11.4.2 Imaging</td><td>• DXA ~~scan (~~ (BMD and BMC) of whole body [less head], ~~including~~ spine, ~~one third~~ and forearm ~~and tibia,~~ (including ultra-distal, mid-distal, and one third radius regions of interest) to assess bone mineral density (BMD) and bone mineral content (BMC).</td></tr>
</table>

Section No./Title	Text Revisions
Rationale #9: **If the 111-901 visit at which the subject chooses to enter Study 111-206 and the 111-206 Screening visit are on the same day, the procedures common to both visits will be performed one time only**	
Table 9.1.1, footnote b	If the 111-901 visit at which the subject chooses to enter Study 111-206 and the 111-206 Screening visit are on the same day, the procedures common to both visits will be performed one time only.
Rationale #10: **On days when PK samples are being drawn, ECG will be performed within a 5 minute window prior to the 30-minute PK assessment**	
Table 9.1.1, footnote h Section 9.11.6.7	On days when PK samples are being drawn, ECGs should be performed within a 5-minute window prior to 30-minute PK assessment.
Rationale #11: **Exclusion criterion #6 has been revised from "…as determined by the Investigator based on the following assessments…) to (…as determined by the Investigator and informed by the following assessments…)**	
Section 9.3.2 Exclusion Criteria	Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator ~~based on~~ and informed by the following assessments
Rationale #12: **Exclusion criterion #15 has been revised to include cervicomedullary decompression surgery (Cohorts 2 and 3 only)**	
Section 9.3.2 Exclusion Criteria	Have ever had cervicomedullary decompression surgery (Cohorts 2 and 3 only), spine or long-bone surgery (i.e., surgery involving disruption of bone cortex) or have ever had bone-related surgery with chronic complications NOTE: Subjects with prior cervicomedullary decompression may be allowed into Cohort 1 only after discussion and agreement with Medical Monitor.
Rationale #13: **Inclusion/exclusion criteria have been added for Cohort 3 subjects enrolling in the observational period**	

Section 9.3.3 Inclusion Criteria for Cohort 3 Observation Period; Section 9.3.4 Exclusion Criteria for Cohort 3 Observation Period	**9.3.3 Inclusion Criteria for Cohort 3 Observation Period** Individuals eligible to participate in this study must meet all of the following criteria: 1. Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, willing and able to provide written assent (if applicable) after the nature of the study has been explained and prior to performance of any research-related procedure. 2. Birth to ≤ 3 months of age at study entry. 3. Have ACH, documented by genetic testing 4. Are willing and able to perform all study procedures as physically possible **9.3.4 Exclusion Criteria for Cohort 3 Observation Period** 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 disorders: • Hypothyroidism • Insulin-requiring diabetes mellitus • Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others) • Inflammatory bowel disease • Autonomic neuropathy 3. Have an unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression 4. Have a history of any of the following: • Renal insufficiency • Anemia 5. Have a history of cardiac or vascular disease, including the following: • Cardiac dysfunction • Hypertrophic cardiomyopathy • Congenital heart disease • Cerebrovascular disease, aortic insufficiency • Clinically significant atrial or ventricular arrhythmias 6. Current treatment 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,

<table>
<tr><th>Section No./Title</th><th>Text Revisions</th></tr>
<tr><td></td><td>drugs known to alter renal function that is expected to continue for the duration of the study
7. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable) in the previous 3 months
8. Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
9. Have used any other investigational product or investigational medical device for the treatment of ACH or short stature
10. Planned or expected bone-related surgery (ie. surgery involving disruption of bone cortex), during the study period.
11. Planned or expected to have limb-lengthening surgery during the study period.
12. Have any condition that, in the view of the Investigator, places the subject at high risk of poor compliance with the visit schedule or of not completing the study.
13. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation</td></tr>
<tr><td colspan="2">Rationale #14:
A table of restricted medications, including growth hormone, has been added</td></tr>
<tr><td>Section 9.3.5 Current Chronic Therapy with Restricted Medications</td><td>9.3.5 Current Chronic Therapy with Restricted Medications
Table 9.3.5.1 lists the medications that are restricted in Study 111-206.
Current Chronic Therapy with Restricted Medications
<table><tr><th>Restricted Medications</th></tr><tr><td>• Antihypertensive medications
• Angiotensin-converting enzyme (ACE) inhibitors
• Angiotensin II receptor blockers
• Diuretics
• Beta-blockers
• Calcium-channel blockers
• Cardiac glycosides
• Systemic anticholinergic agents
• GnRH agonists
• Growth hormone (and analogs)
• Any medication that may impair or enhance compensatory tachycardia, diuretics, or other drugs known to alter renal or tubular function</td></tr></table></td></tr>
</table>

Section No./Title	Text Revisions
	• Any medication that in the investigator's judgment, may compromise the safety or ability of the subject to participate in the clinical trial
Rationale #15: **Genomic Biomarker Analysis, the text "of plasma DNA" has been removed from "Exploratory genomic analysis of plasma DNA may inform understanding of the BMN 111 mechanism of action…"**	
Section 9.11.4.4 Genomic Biomarker Analysis	Exploratory genomic analysis ~~of plasma DNA~~ may inform understanding of the BMN 111 mechanism of action in achondroplasia.
Rationale #16: **For subjects enrolled in Cohort 3 (0 to < 6 months old), the collection period for all AEs begins after informed consent is obtained**	
Table 9.1.2 footnote h Section 10.2.1 Adverse Event Reporting Period	For subjects enrolled in Cohort 3 (0 to < 6 months old), ~~AE~~ the collection period for all AEs begins after ~~screening~~ informed consent is obtained.
Rationale #17: **Administrative updates have been made to improve consistency and clarity**	
#17a: **Text has been changed to reflect the age of majority rather than age 18, as the age of majority varies between countries**	
Section 5.3 Subject Information and Informed Consent	Subjects under the age of ~~18 years~~ majority will provide written assent (if required), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects. The Investigator will provide copies of the signed ICF to
#17b: **Section 7.3 has been updated to include a description of Study 111-302**	
Section 7.3.5 Study 111-302	**7.3.5 Study 111-302** Study 111-302 is an open-label Phase 3 extension study to further evaluate the efficacy and safety of BMN 111 either until subjects reach near-final adult height (defined as evidence of growth plate closure and < 1.5 cm/yr annualized growth velocity), or for 5 years if near final adult height (NFAH) occurs prior to the end of the 5-year period. All subjects will receive BMN 111 15 µg/kg. This study will allow for long term assessment of the effect of daily BMN 111 administration on safety, tolerability, growth velocity, height, and body proportions in subjects who have completed 1 year of placebo or BMN 111 treatment in Study 111-301.
#17c: **The secondary objective addressing evaluation for hip, thigh, or knee pain, or change in gait has been**	

Section No./Title	Text Revisions
revised to clarify that hip assessments are performed at screening, and these measures serve as a baseline for future assessments	
Section 8 Study Objectives	• Evaluate for hip, thigh, or knee pain, or change in gait ~~from medical history~~
#17d: **Error in Section 9.1, description of Cohort 3 has been corrected to state that at least *17* additional subjects will be randomized**	
Section 9.1 Overall Study Design and Plan	Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least ~~20~~ 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation
#17e: **Clarification about age-appropriate dose adjustment has been added to indicate that subjects will be administered the recommended dose appropriate to their current age**	
Section 9.1.1 Overall Study Design and Plan Section 9.1.1 Dose Adjustments	As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥ 24 to < 60 months.
#17f: **The time window for the Week 56 safety follow-up visit has been changed from ± to + 7 days to allow a full 4 weeks between the last dose of study drug and the safety follow-up visit**	
Table 9.1.1 Section 12.1.10 Week 56 Safety Follow-up	Week 56 Safety Follow-Up ~~(±~~ (+ 7d) 12.1.10 Week 56 Safety Follow-up ~~(±~~ (+ 7d)
#17g: **Clarified that the screening/baseline hip assessment includes a pelvis x-ray**	
Table 9.1.1 Section 12.1.1 Screening/Baseline Day -30 to Day -1	Screening baseline hip assessment with pelvis x-ray
#17h: **Because the definition of ACH-related events differed between sites, capture of ACH-related events**	

Section No./Title	Text Revisions
has been changed to capture all procedures listed in the Schedule of Events to ensure all procedures are collected and analyzed	
Tables 9.1.1 and 9.1.2 Section 9.11.6.2	Capture ~~achondroplasia related~~ all procedures in the Schedule of Events **9.11.6.2 Procedures ~~due to Achondroplasia~~ During the Study**
Sections 12.1.2-12.1.11; Sections 12.2.2-12.2.3	• Capture all procedures
#17i: **Vital signs instructions now include sitting or supine positions to account for subjects who are too young to sit. The duration of vital signs assessments in Section 9.11.6.5 and Table 9.11.6.5.1 has been extended to align with the assessments presented in the SOE. Additionally, if a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1,2 schedule.**	
Table 9.1. Vital Sign Frequency Table	After at least 5 min of rest, subject's vital signs are taken, preferably in sitting or supine position. 1. Vital sign measurements are taken once per time point, preferably in a sitting or supine position, after at least 5 minutes of rest. 8. If a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1,2 schedule.
Section 99.11.6.5 Vital Signs, Physical Examinations and Other Observations Related to Safety	Vital signs assessed pre-dose will include seated or supine 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)… 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.~~ or supine position. Vital sign measurements should be repeated and documented 3 times, with at least 5-minute intervals between assessments… At other visits, vital sign measurements are taken once per time point in a sitting or supine position after at least 5 minutes of rest.
Table 9.11.6.5.1 Vital Sign Frequency Table	Please see tracked change version of Table 9.11.6.5.1 at the end the document.
#17j: **In the event that a sentinel subject has an interrupted dose of study drug on Day 1, instructions have been included for a change in the PK collection schedule.**	

Section No./Title	Text Revisions
Table 9.1.1 footnote L Section 9.11.5 Pharmacokinetics Variables	In the event of interruption of study drug administration for a sentinel patient on Day 1 when PK samples are scheduled, the collection of PK samples should be delayed until the subsequent day and only performed after successful administration of study drug has been completed in a single injection.
#17k: **Footnote m in Table 9.1.1 has been updated to correspond to the information in Section 9.11.6.10, *Anti-BMN 111 Immunogenicity Assessments and IgE Testing***	
Table 9.1.1 footnote m	m. Antibodies: Total anti-BMN 111 (TAb), TAb cross-reacting with endogenous natriuretic peptides, and neutralizing antibody (NAb) samples (serum) will be drawn pre-dose at each time point listed on the SOE. TAb cross-reacting with endogenous natriuretic peptides and NAb testing will be performed only on baseline and TAb positive samples from subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg.
#17l: **In Table 9.1.1, footnotes n and o, and Section 9.11.3, *Secondary Efficacy Variables*, text has been added to specify the biomarkers used to assess changes in bone and collagen metabolism**	
Table 9.1.1 footnotes n and o	Table 9.1.1 footnotes n and o
Section 9.11.3 Secondary Efficacy Variables	Section 9.11.3 Secondary Efficacy Variables
#17m: **In Table 9.1.1 footnote q, instruction has been included that efforts to obtain a satisfactory MRI image can be discontinued after 3 unsuccessful attempts.**	
Table 9.1.1 footnote q	Efforts to obtain a satisfactory image can be discontinued after 3 unsuccessful attempts.
#17n: **In Table 9.1.1, footnote v now includes instructions for managing a dose interruption.**	
Table 9.1.1 footnote v	If interruption of study drug injection occurs, the remainder of the assigned dose should be administered immediately (and no later than within 5 minutes) in a different location. The same syringe should be used and newly reconstituted investigational drug should be used to draw the remainder of the dose.

Section No./Title	Text Revisions
#17o: **Section 9.1.1, *Dose Adjustments*, has been corrected to state that a DMC review will occur after the third sentinel subject reaches Week 12 post-dose adjustment**	
Section 9.1.1 Dose Adjustments	The remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. After the third sentinel subject reaches ~~day 30~~ Week 12 post dose adjustment
#17p: **In Section 9.3.8, *Duration of Subject Participation*, final follow-up visit for subjects who discontinue from the study has been changed from 2 weeks to 4 weeks**	
Section 9.3.8 Duration of Subject Participation	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 ~~2~~ 4 weeks after their last study visit
#17q: **In Section 9.4.1, *Treatments Administered*, text has been added to reiterate that sentinel subjects will be treated with BMN 111, versus randomized subjects who will receive either BMN 111 or placebo. Additionally, the BMN 111 dose level is subject to potential per-protocol adjustment.**	
Section 9.4.1 Treatments Administered	~~Subjects~~ Sentinel subjects will receive BMN 111 at a daily dose of 15 µg/kg (subject to adjustment per protocol). Randomized subjects will be randomized to BMN 111 at a daily dose of 15 µg/kg (subject to adjustment per protocol) or placebo for the duration of the study.
#17r: **Directions for subject observation following BMN 111 administration at study visits has been revised in Section 9.4.1.1, *Study Drug Administration*, for consistency with Section 9.4.4, *Directions for Administration***	
Section 9.4.1.1 Study Drug Administration	During the study, BMN 111 or placebo will be administered as a single 15 µg/kg SC injection given daily at approximately the same time each day whenever possible. Determination of appropriate injection sites will be left to the discretion of the investigator. The same injection site should not be used 2 days in a row, and sites should be rotated ~~between the 4 injection sites~~. Study drug should be administered at age-appropriate locations (upper thigh, upper back of arm, abdomen or buttocks). Doses may be administered in any of the common SC areas (upper arm, thigh, abdomen, buttocks). Following administration of each dose at clinic visits, subjects ~~will~~ should be observed for ~~at least 2~~ 8 hours after the injection ~~for~~ on Days 1 ~~to 3,~~ and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes ~~for all other days of dose administration (longer if clinically indicated) either in~~ after every injection that is not administered at the clinic ~~by study personnel, by a home health nurse, or by a parent/caregiver~~.

Section No./Title	Text Revisions
#17s: **Text in Section 9.4.1.1, *Study Drug Administration* now indicates that study drug injections will be administered at age-appropriate sites, determined at the discretion of the investigator**	
Section 9.4.1.1 Study Drug Administration	During the study, BMN 111 or placebo will be administered as a single 15 µg/kg SC injection given daily at approximately the same time each day whenever possible. Determination of appropriate injection sites will be left to the discretion of the investigator.
#17t: **Text has been revised to indicate that in the hour prior to injection, all subjects should be well hydrated and fed.**	
Section 9.4.4 Directions for Administration Section 9.6 Dietary or Other Protocol Restrictions	Subjects should have adequate food intake prior to dosing. ~~n the hour prior to injection, all~~ All subjects should have been well hydrated and fed in the hour prior to administration of BMN 111 or placebo.
#17u: **In Section 9.4.5, *Method of Assigning Subjects to Treatment Groups*, a note has been added that in Japan, subjects are randomized separately within each cohort.**	
Section 9.4.5 Method of Assigning Subjects to Treatment Groups	NOTE: In Japan, subjects are randomized separately within each cohort.
#17v: **Section 9.11.4.2, Imaging Assessment Procedures, has been corrected by removing lateral views from bilateral lower extremity x-rays, and clarified to state that bilateral lower extremity x-rays, anterior-posterior (AP) view, are done to assess growth plate morphology. Instruction has been added to contact the medical monitor to discuss alternate non-radiological methods for assessment if there are IRBs or IECs unwilling to allow x-rays in Cohort 3 subjects (also, Table 9.1.1, footnote t). Additionally, the list of DXA acquisitions has been clarified.**	
Table 9.1.1 footnote t	Although X-rays are preferable for consistency across the study population, if there are IRBs or IECs unwilling to allow x-rays in Cohort 3 subjects, contact the MM to discuss alternate non-radiological methods for assessment.
Section 9.11.4.2 Imaging Assessment Procedures	• Bilateral lower extremity x-rays ~~including both~~, anterior-posterior (AP) ~~and lateral views~~ view, to assess growth ~~plates.~~ plate morphology. • Hip imaging via pelvis x-ray to identify hip pathology (if changes from baseline trigger further evaluation) • Lumbar spine x-rays to measure changes from baseline in bone morphology and pathology.

Section No./Title	Text Revisions
	• MRI to evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions. • DXA ~~scan (~~ (BMD and BMC) of whole body [less head], ~~including~~spine, ~~one third~~ and forearm ~~and tibia,~~ (including ultra-distal, mid-distal, and one third radius regions of interest) to assess bone mineral density (BMD) and bone mineral content (BMC). Although X-rays are preferable for consistency across the study population, if there are IRBs or IECs unwilling to allow x-rays in Cohort 3 subjects, contact the medical monitor to discuss alternate non-radiological methods for assessment.
#17w: **Section 9.11.4.7.1, *Bayley-III*, has been revised to remove reference to the Social-Emotional and Adaptive Behavior Scale components because these scales will not be used in this study. Additionally, the duration of the assessment has been clarified.**	
Section 9.11.4.7.1 Bayley-III	Scales include Cognitive subscale, Receptive and Expressive subscales, and Gross and Fine Motor subscales. The two language scales make up a composite Language Scale score and the Gross and Fine Motor subscales yield a composite Motor Scale score. ~~In addition, there is a Social-Emotional Scale and Adaptive Behavior Scale, which is a questionnaire read and completed by parent or caregiver.~~ In addition to its use for subjects ranging from 1 to 42 months old, the Bayley-III assessment will be administered to those entering the study between 42 and 60 months old (Figure 9.11.4.7.1) and for the remainder of the duration of this study.
#17x: **In Section 9.11.4.7.4, *Child Behavior Checklist*, the duration of the assessment has been clarified.**	
Section 9.11.4.7.4 Child Behavior Checklist	The Child Behavior Checklist (CBCL) is for use in children from 1.5-5 years old, and will be administered for those entering the study at less than 5 years old and for the remainder of the duration of the study.
#17y: **In Section 10.1.2, the statement that hospitalization for less than 24 hours will not be considered an SAE has been deleted to make the criterion consistent across all BioMarin protocols. Section 10.1.2, *Serious Adverse Events*.**	
Section 10.1.2 Serious Adverse Events	Requires or prolongs inpatient hospitalization~~. Hospitalization for less than 24 hours will not be considered to be an SAE.~~

Section No./Title	Text Revisions
#17z: **Error in Table 10.2.3.3.1 has been corrected to read "The AE could not be explained by factors or causes other than exposure to the IP"**	
Table 10.2.3.3.1	• The AE could ~~possibly~~ not be explained by factors or causes other than exposure to the IP

Table 9.11.6.5.1 Vital Sign Assessment Frequency (tracked changes)

Vital Sign Assessment Frequency ~~Pre-Dose~~				
Screening	After at least 5 min of rest, subject's ~~BP is~~ vital signs are taken, preferably in sitting or supine position. ~~Then the subject will stand~~ Vital sign measurements should be repeated and ~~BP will be taken again~~ documented 3 times with at ~~approximately 1 and 3 minutes after standing.~~ least 5 min intervals between assessments.			
~~All other visits~~	~~After at least 5 min of rest, subject's BP is taken 1 time in sitting position~~			
	Assessment Frequency ~~Post-Dose~~			
Dosing Visits	**0-1 hr post-dose**	~~1~~ **0-2 hr post-dose**	**2-4 hr post dose**	**4-8 hr post-dose**
Days 1~~Day~~, 2~~–3~~		~~Q15~~ q 15 min ~~((± 5 min)Q30 min ((±~~ (± 5 min)	~~Q~~ q 30 min (± 5 min)~~Q30 min ((± 5 min)~~	q 60 min (± 10 min)
Days 3, 8		q 15 min (± 5 min)	q 30 min (± 5 min)	
Subsequent dosing visits	q 15 min (± 5 min); final assessment prior to end of visit (if longer than 1 hr)			
1. ~~All other dosing visits: vital~~ Vital sign measurements are taken once per time point, preferably in a sitting or supine position, after at least 5 minutes of rest. 2. Heart rate, blood pressure, and respiratory rate should	~~Q 30 min (± 5 min); for 1 hour~~			

be taken and recorded at each indicated time point. 3. When blood samples and vital sign assessments are scheduled at the same time or within the same time window, vital signs should be measured before blood samples are drawn. 4. If a vital sign measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and wait several minutes before measuring vital signs. 5. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated. 6. If a subject has a hypotensive event, or signs potentially consistent with hypotension, or a decrease of 20 mm Hg systolic BP or more from baseline (defined by pre-dose vitals collected that day), vital signs should be measured and recorded approximately every 15 minutes (± 5 minutes) for the first hour and every 30 minutes (± 5 minutes) thereafter until the BP returns to		

baseline (or within the normal range for this subject as defined by PI) and signs (if present) resolve. 7. If the decision is made to adjust the dose, vital signs will be obtained for at least 4 hr following the first dose at the adjusted dose level, similar to the Day 3, 8 schedule. 8. If a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1,2 schedule.		

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months
Protocol Number:	111-206
Active Investigational Product:	BMN 111 (modified rhCNP)
IND	111299
European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2016-003826-18
Indication:	Achondroplasia
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 2
Sponsor's Responsible Medical Monitor:	PI , MD PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Study Design:	Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH
Treatment Duration	52 weeks
Duration of Subject Participation:	60 weeks for Cohorts 1 and 2 (screening, treatment, follow-up). Subjects in Cohort 3 who enter the study for a 12-week observational period will participate for approximately 70 weeks (screening, observational period, treatment, follow-up)
Dose:	15 µg/kg BMN 111 or placebo daily, subject to adjustment per protocol
Study Population:	Children 0 to < 60 months old with achondroplasia
Date of Original Protocol:	06 December 2017
Date of Amendment 1:	16 August 2018
Date of Amendment 2:	08 February 2019

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 2

Date: 08 February 2019

RATIONALE AND SUMMARY OF MAJOR CHANGES

The protocol has been amended to include the following changes:

1. The following exploratory objectives have become secondary objectives in Amendment 2. [§8.0]
    - Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower segment ratio.
    - Evaluate the effect of BMN 111 on sleep apnea
    - Evaluate the effect of BMN on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
    - Describe the incidence of surgical interventions, including cervical decompression, adenotonsellectomy, and typanostomy

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

2. The secondary imaging assessment procedures, excluding the MRI assessment, have been moved to the secondary safety variables section. The hip imaging assessment has been removed, the X-ray assessment has been modified to include long bone growth, and the DXA assessment will no longer include the forearm. Also, the paragraph discussing the possibility of non-radiological methods of assessment for subjects in Cohort 3 has been deleted. [§9.12.6.3]

Rationale: Imaging assessments, excluding MRI, evaluate the safety of BMN-111 by identifying bone pathologies, morphologies, BMD, and BMC. The pelvis X-ray assessment has been removed to reduce the subjects' radiation burden, because the femoral head is captured on X-rays of the lower extremities. DXA of the forearm has also been removed. Thus, concerns regarding excess radiological exposure have been addressed.

3. The MRI assessments remain as a subsection in the Secondary Efficacy Variables section. [9.11.2]

Rationale: MRIs evaluate the effect of BMN 111 on skull and brain morphology, an efficacy variable.

4. The screening baseline hip assessment with pelvis X-ray has been removed from the Schedule of Events [Table 9.1.1]

Rationale: Eliminating the pelvis X-rays at the screening visit will help minimize the radiation burden on study subject.

5. Footnotes have been changed to modify procedures and to add early termination visits (ETV) for anthropomorphic measurements, DXA, and X-rays [Table 9.1.1]

Rationale: The changes in ETV for have been made to align 111-206 with other studies in the clinical program. Changes in the X-ray and DXA procedures also help minimize the radiation burden on the study subjects.

6. The Child Behavior Checklist has been moved from §4.12.3.3 Clinical Outcome Assessments to be a subsection of §9.12.6 Safety Variables [§9.12.6.6]. A sentence specifying that the CBCL should be given prior to other study assessments was added.

Rationale: The CBCL checklist addresses symptoms related to issues of safety (eg, sleep problems, aggressive behavior) rather than efficacy. It is thought that the answers to the CLCL, as a Patient Reported Outcome instrument, may be affected by the study procedures.

7. The following sentence was added to §9.3.3 and §9.3.4 "After completing the observation period, subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug."

Rationale: Cohort 3 subjects have different eligibility criteria during the observational period, thus Cohort 3 subjects who complete the observation period must also fulfill the general eligibility criteria before receiving treatment.

8. Mention of sterile diluent for reconstitution of BMN 111 has been deleted. [§9.4.2.1]

Rationale: Only sterile water for injection is provided for reconstitution of drug product.

9. The secondary efficacy variables were updated. [§9.12.3]

Rationale: The secondary efficacy variables were updated to match the changes in secondary endpoints.

10. Additions and corrections have been made to the PK parameters to be estimated by non-compartmental analysis. [§9.12.5]

Rationale: Clarification that PK parameters for both sentinels and study subjects will be analyzed, as well as the addition of C_{max} and T_{max} to the PK parameters.

11. Updates have been made §13 Data Quality Assurance and §17 Case Report Forms and Study Documents.

Rationale: Language required in the current BioMarin protocol template was added.

12. The identity of the medical monitor has been updated to George S. Jeha [§10.8].
13. Administrative changes have been made throughout the amended protocol for consistency, accuracy, and clarity.

Refer to Section 24 for a summary of revisions to Amendment 1 (dated 13 August 2018).

2 SYNOPSIS

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

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

PROTOCOL NUMBER: 111-206

STUDY SITES: Approximately 10-15 sites worldwide

PHASE OF DEVELOPMENT: Phase 2

STUDY RATIONALE:

BMN 111 is a recombinant CNP analogue that has been engineered to resist degradation by NEP, allowing for a longer half-life.

The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ (TD) model (Lorget, 2012), and a milder [Ach] /+ (Ach) model. These included studies in 7-day old TD mice given BMN 111 daily by SC administration for up to 20 days and a study in 3-week old Ach mice given BMN 111 daily by SC administration for 5 weeks. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. In wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels (Wendt, 2015). Additionally, the potential effect of age on BMN 111 PK was evaluated in normal rats aged between 7 days and 12-13 weeks.

Infants and young children with ACH have a high incidence of medical complications and currently there is no approved pharmacological therapy for ACH in the US or EU. The most severe complication, cervicomedullary compression (CMC), occurs in a subset of subjects with ACH due to abnormal endochondral bone growth and narrowing of the foramen magnum (White, 2016). CMC has been linked to serious respiratory and neurological complications including hypotonia, apnea, ataxia, developmental delay, and respiratory arrest associated with sudden death (Mukherjee, 2014). Foramen magnum decompression surgery is currently the only treatment for this condition.

Sleep apnea has also been extensively described in ACH, and sleep-disordered breathing may affect up to 85% of all children with ACH (Ireland, 2012). This is thought to be due to midface hypoplasia, relative adenotonsillar hypertrophy, and potential posterior cranial fossa compression secondary to abnormal endochondral bone growth. Sleep apnea in ACH not only results in the need for surgical intervention, but has also been linked to sudden death in rare cases (Pauli, 1984).

Similarly, the dysregulation of endochondral bone growth in ACH leads to other medical complications which are prevalent in this subject population, such as the following:

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

- Spinal stenosis, kyphosis, and lordosis (secondary to altered growth plate ossification in the vertebrae and narrowing of the interpedicular distances) (Shirley, 2009)
- Developmental delay of gross motor and ambulatory skills (associated with proximal limb shortening, macrocephaly, and hypotonia) (Ireland, 2010)
- Delayed functional skills and increased need for caregiver assistance (eg, eating, bladder management, bowel management, transfer to chair, climbing stairs) (Ireland, 2011)

BMN 111 was first tested in humans in Study 111-101, a Phase 1 double-blinded, placebo-controlled clinical trial of the safety and tolerability of BMN 111 in healthy adult male volunteers without ACH. Part 1 examined a series of single subcutaneous doses (5 µg/kg, 10 µg/kg and 15 µg/kg), and Part 2 included 10 days of either fixed dosing or dose escalation (0.5 µg/kg to 8 µg/kg). BMN 111 was generally well tolerated at all doses. As expected, mild, transient, self-limited hypotension was reported (refer to current Investigators Brochure for additional information). Following SC administration, BMN 111 was rapidly absorbed with maximal plasma concentrations achieved in less than 30 minutes. BMN 111 was rapidly cleared from the plasma with a mean $t_{1/2}$ ranging from 40 to 55 minutes across dose levels. BMN 111 exposure (C_{max} and AUC_{0-t}) generally increased greater than proportional to the increase in dose across the 2.5-to-15 µg/kg dose range. Exposure following multiple dosing was found to be similar to exposure following single doses, indicating no apparent accumulation or time-dependence with once-daily SC administration.

Study 111-202, the second clinical trial in humans and the first in children with ACH, is an ongoing Phase 2, open-label, sequential-cohort, dose-escalation study that assesses daily SC BMN 111 in pediatric subjects with ACH aged 5-14 years with doses ranging from 2.5 µg/kg to 30 µg/kg. The primary objective of Study 111-202 is to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months; the secondary objectives are to determine change from baseline in annualized growth velocity (AGV), growth parameters, body proportions, and evaluate the pharmacokinetics (PK) of BMN 111 in children with ACH.

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

Analysis of safety data from the 6 month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at the doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated (refer to current Investigator's Brochure for specific details). One subject (30 µg/kg) in 111-202 withdrew due to an AE. The subject developed non-serious, asymptomatic Grade 1 intermittent Wolff-Parkinson-White pattern, which was discovered on a routine day 10-study monitoring ECG. The most common AEs across all cohorts were injection site reactions, asymptomatic hypotension, headache, and nasopharyngitis. Based on previous experience of the ongoing Phase 2 clinical trial, including the 24 month data cut at 15 µg/kg, injection site reactions have been identified as risks associated with BMN 111 injections. The majority of hypotension events were grade 1 and reported in the setting of routine BP measurement. All reported events of hypotension were transient and resolved without medical intervention. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

Analysis of efficacy data from the 6 month initial phase of Study 111-202 showed that subjects treated with BMN 111 for 6 months at doses ranging from 2.5 15 µg/kg daily had a dose-dependent improvement in AGV, with ~50% improvement in AGV seen at the 15 µg/kg dose. The data from Cohort 4 (30 µg/kg) show an apparent greater than dose-proportional increase in BMN 111 plasma exposure (C_{max} and AUC_{0-t}), 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).

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are 0 to < 60 months old. This 52-week study will enable assessment of BMN 111 efficacy and safety, tolerability, pharmacodynamics biomarkers, and PK in this population. Additional exploratory endpoints pertaining to medical complications of ACH will also be evaluated.

Efficacy/toxicity studies have been conducted in neonatal and very young animals (7 day postpartum mouse and rat) in both a disease (TD mouse) and non-disease (rat) model. Given that this is the first study in infants and young children, an age based cohort study design is used to assess safety and PK in young children (Cohort 1, ≥ 24 to < 60 months) prior to dosing toddlers (Cohort 2, ≥ 6 to < 24 months) and infants (Cohort 3, 0 to < 6 months). PK will be monitored and evaluated; Day 1 PK data from the sentinel subjects will inform dose selection modification for the sentinel subjects and for the rest of the cohort to target the observed exposure of the 15 µg/kg dose group in Study 111-202. Safety, efficacy and PK data from Study 111-202, a Phase 2 study in children with ACH, where a dose of 15 µg/kg has been and continues to be studied, are expected to be the most relevant, and translatable to this study (111-206).

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

OBJECTIVES:

The primary objectives of the study are to:

- Evaluate the safety and tolerability of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate the effect of BMN 111 on change from baseline in length/height Z-score

The secondary objectives of the study are to:

- Evaluate the effect of BMN 111 on change from baseline in AGV throughout the 52 weeks of the study
- Evaluate the effect of BMN 111 on bone morphology/quality by X-ray and dual X-ray absorptiometry (DXA)
- Evaluate the PK of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of BMN 111 on health-related quality of life (HRQoL), developmental status, and functional independence using age-specific QoL and functional independence questionnaires (Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III], Activity of Daily Living and Functional Independence Measure (Wee-FIM), Infant Toddler Quality of Life Questionnaire (ITQOL), Child Behavior Checklist (CBCL)
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of BMN 111 on bone metabolism and BMN 111 pharmacodynamic biomarkers
- Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower segment body ratio
- Evaluate the effect of BMN 111 on sleep apnea
- Evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

The exploratory objectives of the study are to:

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

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

STUDY DESIGN AND PLAN:

This study, 111-206, is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH.

Study 111-901 is an ongoing study to collect serial growth measurements on pediatric subjects with ACH who are being considered for subsequent enrollment in future BioMarin studies. Subjects who are age ≥ 6 months to < 60 months old; who have documented ACH confirmed by genetic testing; at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before screening; and who meet the study eligibility criteria, will participate. Eligible subjects ranging from 0 months to < 3 months old may enroll directly into 111-206 and have a minimum of 3 months of pretreatment observation prior to commencing treatment with investigational product, or may enroll in 111-901 for a minimum of 3 months of pretreatment growth assessment immediately before roll-over to 111-206.

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

The primary objectives of this study are to assess the safety and tolerability of daily SC BMN 111 administered to infants and young children with ACH, and to evaluate the effect of BMN 111 on length/height Z-score. Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive BMN 111, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who will be under observation or receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

If subjects who enroll in Cohort 3 are not able to begin treatment by <6 months of age, they will continue in the pretreatment period for another 3 months before enrolling in Cohort 2 to fulfill the pretreatment requirement for Cohort 2.

Sentinel subjects from each cohort will be enrolled, treated with BMN 111, and studied for short-term safety and PK data. No two sentinel subjects will be dosed on the same day for any cohort. After the sentinel data are evaluated additional recruited subjects will be randomized to receive BMN 111 or placebo SC daily (1:1 ratio) for 52 weeks.

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At the start of the study, 3 sentinel subjects will be enrolled and monitored in Cohort 1. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 1 (≥ 27 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a data monitoring committee (DMC) review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort (Cohort 2) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 2. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 2 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the youngest cohort (Cohort 3) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 3. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 3 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio).

Cohort 3 subjects must have a minimum of 3 months of observation prior to commencement of treatment. These subjects will have the option to enroll in either 111 901 or 111-206.

Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

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As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥24 to <60 months. Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in all treatment groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term; and to study the long-term outcomes on sustained growth, proportionality, bone maturation and medical comorbidities.

For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

Data Monitoring Committee (DMC)

In addition to safety and PK 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. After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort will be opened and the 3 sentinel subjects will be enrolled.

The DMC will make recommendations for stopping or continuing the study on an individual subject level and/or on a cohort level per the pre-specified stopping criteria. Based on criteria outlined in the protocol, the DMC may also make endorsements for dose adjustments if needed.

Please see DMC Charter for further details.

Individual Subject Stopping Criteria

For individual subjects treated with BMN 111, DMC will be informed if any of the following individual subject stopping criteria should occur. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the individual subject will be considered.

- Any treatment-emergent adverse event (AE) assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (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

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- Clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec
- Clinically significant new or worsening signs of cervicomedullary compression as determined by the Investigator and in consultation with Sponsor medical monitor and neurosurgical specialist (if needed)
- Adverse findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as determined by the Investigator and in consultation with Sponsor Medical Monitor and orthopedic specialist (if needed)

If the subject meets any stopping criterion, 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 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
- Permanent treatment discontinuation (with an option of ongoing assessment in the study)

Cohort Stopping Criteria

For each cohort, a DMC review will be conducted if any of the following cohort stopping criteria occur in subjects treated with BMN 111. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the cohort(s) will be considered and the impact on all other age cohorts will be assessed.

- Any treatment-emergent AE assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have a treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any two subjects cohort have a Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Any two subjects have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec

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- Any two subjects have adverse 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)

Dose Adjustments

Analysis of available PK data from studies 111-101 and 111-202 indicated that differences in subject body weight did not directly translate to differences in total body clearance of BMN 111. The same weight-based dose in the pediatric population of Study 111-202 (5-12 years old) yielded lower exposure (C_{max} and AUC) than that characterized in the adult population of Study 111-101. Therefore, the same weight-based dose in the young pediatric population in this study may yield exposure less than the target exposure range characterized to be safe and effective in Study 111-202 at the 15 µg/kg dose. Since this is the first experience with BMN 111 in this young pediatric population, it is also possible the exposure at 15 µg/kg could be greater than the target exposure range, and dose adjustment may be warranted. Thus, an option for adjustment of the weight-based dose is provided to ensure that the appropriate target exposure for safety and efficacy is reached for the young subjects in this study.

The need for dose adjustment will be evaluated as follows: three sentinel subjects in Cohort 1 will receive an initial dose of 15 µg/kg. After all three sentinel subjects reach Day 8, a review will occur to evaluate all available safety and PK data (at minimum). If the criteria for dose adjustment are met, the three sentinel subjects will be started on the new adjusted dose at their next scheduled visit, and vital signs will be obtained for at least 4 hours post-dose.

The remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. After the third sentinel subject reaches Week 12 post-dose adjustment, a DMC review will occur to evaluate all safety and PK data and, upon endorsement, the three sentinel subjects from the next younger cohort will be enrolled starting at the new adjusted dose. The three sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥ 24 to < 60 months.

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Safety and Efficacy Monitoring

Each treated subject will have expanded outpatient safety monitoring for a minimum of 3 days of dosing, during which they will be closely observed and non-invasive hemodynamic monitoring will be conducted for at least 4-8 hours post-dosing. Because younger children may not be able to verbalize complaints of dizziness or lightheadedness that are potentially associated with hypotension, study personnel and caregivers will be trained to recognize the signs of hypotension in this population, which may include tachycardia, pallor, diaphoresis, lethargy, delayed capillary refill, and poor feeding. Appropriate rigorous training will be required for parents and caregivers prior to daily injections at home. Training includes the storage, reconstitution, and administration of BMN 111, as well as documentation/reporting of AEs and vigilance for signs of hypotension.

It is generally expected that after subjects are tolerating the drug well and specified criteria have been met, caregivers will begin administering study drug. Home health care is not required at any point but may be provided if the caregiver is unable or unavailable to administer the study drug. A Home Healthcare nurse will train the caregiver(s) if training has not been completed by the Day 3 visit. A phone call by the study staff member to the caregiver will be required weekly for 6 months and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. If the caregiver cannot be contacted by phone after two attempts, contact can be made via email.

Safety will be evaluated by the incidence of AEs, serious AEs (SAEs), X-rays will be performed of the entire lower extremities and spine to evaluate for changes in bone morphology and growth, laboratory test results (urinalysis, chemistry, and hematology), vital signs, physical examination, ECG and echocardiogram, hip clinical assessment, and anti-BMN 111 immunogenicity assessments. Clinical laboratory tests, PK, immunogenicity and blood biomarker assessments will be limited to the minimum necessary for evaluation of safety and efficacy in order to minimize blood volume in the pediatric population.

Efficacy will be assessed by change from baseline in AGV and length/height Z-score. Secondary assessments will include change from baseline in growth parameters and body proportions by anthropometry. An MRI will be performed to assess the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular, and brain parenchymal dimensions. A board-certified, fellowship-trained (or equivalent) pediatric anesthesiologist will administer anesthesia during MRI measurements in the event that the subject is unable to remain still for the duration of the scan. Sleep studies will be conducted to evaluate sleep apnea. Additional assessments will be conducted to evaluate changes from baseline in bone metabolism and BMN 111 pharmacodynamic biomarkers, and developmental/functional status.

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NUMBER OF SUBJECTS PLANNED:
Approximately 70 subjects, including at least 30 subjects in Cohort 1, at least 20 subjects in Cohort 2, and at least 20 subjects in Cohort 3.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Diagnosis of ACH, confirmed by genetic testing. If subjects had previous genetic testing, subjects must have a lab report from a certified laboratory with the study specific mutation documented.
2. Age 0 to < 60 months, at study entry (Day 1)
3. Cohort 1 and 2 subjects must have at least a 6-month period of pretreatment growth assessment in Study 111-901 immediately before screening and have one documented measurement of height/body length a minimum of 6 months prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrollment in Study 111-901 or (2) via enrollment in this Study 111-206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment.
4. Parent(s) or guardian(s) (and the subjects themselves, if required by local regulations or ethics committee) 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
5. Willing and able to perform all study procedures as physically possible
6. Parent(s) or caregiver(s) are willing to administer daily injections to the subjects and complete the required training

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

1. Have hypochondroplasia or short-stature condition other than achondroplasia (e.g., trisomy 21, pseudoachondroplasia, etc.)
2. Subject weighs < 5.0 kg (Cohorts 1 and 2) or < 4.0 kg (Cohort 3; treatment phase)
3. Have any of the following:
    - Hypothyroidism or hyperthyroidism
    - Insulin-requiring diabetes mellitus
    - Autoimmune inflammatory disease (including celiac disease, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, etc.)
    - Inflammatory bowel disease
    - Autonomic neuropathy
4. Have a history of any of the following:

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- Renal insufficiency defined as serum creatinine > 2 mg/dL
- Chronic anemia or Hgb < 10.0 g/dL (based on screening clinical laboratory testing)
- Baseline systolic blood pressure (BP) below age and gender specified normal range or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms e.g., dizziness, fainting) or recurrent symptomatic orthostatic hypotension
- Cardiac or vascular disease, including the following:
    - Cardiac dysfunction (abnormal echocardiogram determined to be clinically significant by PI and medical monitor) at Screening Visit
    - Hypertrophic cardiomyopathy
    - Pulmonary hypertension
    - Congenital heart disease with ongoing cardiac dysfunction
    - Cerebrovascular disease
    - Aortic insufficiency or other clinically significant valvular dysfunction
    - Clinically significant atrial or ventricular arrhythmias

5. Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening ECG
6. Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator and informed by the following assessments:
    - Physical exam (eg, neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins)
    - Polysomnography (eg, severe central sleep apnea)
    - MRI indicating presence of severe CMC or spinal cord damage
7. Have an unstable medical condition likely to require surgical intervention in the next 6 months, or planned spine or long-bone surgery (i.e., surgery involving significant disruption of bone cortex) during the study period
8. Have documented uncorrected Vitamin D deficiency: 25(OH)D ≤ 15 ng/mL (37.5 nmol/L)
9. Require any other investigational product prior to completion of the study period
10. Have received another investigational product or investigational medical device within 30 days prior to the Screening visit
11. Have used any other investigational product or investigational medical device for the treatment of achondroplasia or short stature at any time
12. Require current chronic therapy with antihypertensive medication or any medication that, in the investigator's judgment, may compromise the safety or ability of the subject to participate in this clinical study (Table 9.3.5.1)

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13. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (> 3 months) at any time
14. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the 12 months prior to screening
15. Have ever had CMC surgery (Cohorts 2 and 3 only), spine or long-bone surgery (ie, surgery involving disruption of bone cortex) or have ever had bone-related surgery with chronic complications
    NOTE: Subjects with prior cervicomedullary decompression may be allowed into Cohort 1 only after discussion and agreement with Medical Monitor.
16. Have ever had limb-lengthening surgery or plan to have limb-lengthening surgery during the study period
17. Have had a fracture of the long bones or spine within 6 months prior to screening
18. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin greater than upper limit of normal at screening (except for subjects with a known history of Gilberts or newborns entering screening in Cohort 3)
19. Have evidence of severe untreated sleep apnea; or have newly initiated sleep apnea treatment (eg, continuous positive airway pressure [CPAP] or sleep apnea-mitigating surgery) in the 2 months prior to screening
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 history of hip surgery or severe hip dysplasia
23. Have a history of clinically significant hip injury in the 30 days prior to screening
24. Have a history of slipped capital femoral epiphysis or avascular necrosis of the femoral head
25. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the Investigator
26. 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
27. Have any concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, for any reason

Inclusion Criteria for Cohort 3 Observation Period

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

1. Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure.

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Also, willing and able to provide written assent (if applicable) after the nature of the study has been explained and prior to performance of any research-related procedure.

2. Birth to ≤ 3 months of age at study entry.
3. Have ACH, documented by genetic testing
4. Are willing and able to perform all study procedures as physically possible

After completing observation period subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug.

Exclusion Criteria for Cohort 3 Observation Period

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 disorders:
   - Hypothyroidism
   - Insulin-requiring diabetes mellitus
   - Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others)
   - Inflammatory bowel disease
   - Autonomic neuropathy
3. Have an unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression
4. Have a history of any of the following:
   - Renal insufficiency
   - Anemia
5. Have a history of cardiac or vascular disease, including the following:
   - Cardiac dysfunction
   - Hypertrophic cardiomyopathy
   - Congenital heart disease
   - Cerebrovascular disease, aortic insufficiency
   - Clinically significant atrial or ventricular arrhythmias
6. Current treatment 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, drugs known to alter renal function that is expected to continue for the duration of the study

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7. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable) in the previous 3 months
8. Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
9. Have used any other investigational product or investigational medical device for the treatment of ACH or short stature
10. Planned or expected bone-related surgery (ie. surgery involving disruption of bone cortex), during the study period.
11. Planned or expected to have limb-lengthening surgery during the study period.
12. Have any condition that, in the view of the Investigator, places the subject at high risk of poor compliance with the visit schedule or of not completing the study.
13. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation

After completing observation period subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug.

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 a 0.8-mg or 2-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 0.8 mg/mL to 2 mg/mL of BMN 111, as well as citric acid, sodium citrate, trehalose, mannitol, methionine, polysorbate 80, and sterile WFI. The target pH of the reconstituted solution is 5.5. Sterile WFI will be commercially sourced. All reconstitution and dose preparation steps will be performed as indicated in the BMN 111 Injection Guide and Injection video.

BMN 111 will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic.

REFERENCE THERAPY, DOSE, ROUTE, and REGIMEN:

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

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

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Placebo will be administered as a single SC injection given daily at approximately the same time each day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic.

DURATION OF TREATMENT: 52 weeks

CRITERIA FOR EVALUATION:

Safety: The following safety outcome measurements will be assessed:

- Incidence of AEs and SAEs
- Imaging assessments (X-rays of the spine and entire lower extremities, DXA of total body less head and spine)
- CBCL
- Vital signs (heart rate, blood pressure, respiratory rate, and temperature)
- Physical examination (including neurological assessment)
- Hip clinical assessment
- Laboratory test results (urinalysis, chemistry, hematology)
- Electrocardiogram (ECG)
- Echocardiogram
- Anti-BMN 111 immunogenicity assessments
- Cortisol levels
- Prolactin levels

Primary Efficacy: The following efficacy outcome measurements will be assessed:

- Safety and tolerability of BMN 111 in children age 0 to < 60 months with ACH
- Change from baseline in length/height Z-score

Secondary Efficacy:

The following measurements will be assessed:

- Change from baseline in AGV
- Change from baseline in upper:lower body segment ratio
- MRI to define skull and brain morphology (including dimensions of foramen magnum, ventricular and brain parenchymal dimensions)
- Sleep study
- Changes in bone and collagen metabolism and BMN 111 pharmacodynamic biomarkers

Clinical outcome assessments:

- Bayley-III
- Wee-FIM

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- ITQOL

Pharmacokinetics: PK sampling will be carried out over the entire study period in sentinel subjects and subjects randomized to BMN 111 or placebo. Whenever possible, the following PK parameters for sentinel subjects and subjects randomized to BMN 111 will be estimated by non-compartmental analysis:

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

Exploratory: The following exploratory measurements will be assessed:

- Clinical photography (optional)
- Optional evaluation of genomic biomarkers

STATISTICAL METHODS:

Sample Size Determination:

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

Safety Analysis:

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 eCRF. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment as assessed by the investigator, seriousness, 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, echocardiogram, hip clinical assessment, and concomitant medication data will also be summarized descriptively. Data summaries will be presented by treatment group (when applicable) for each cohort and overall. All safety results will be listed.

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Efficacy Analysis:

Efficacy variables, including AGV (based on length/height) and length/height Z-score according to normal reference standards (not ACH), along with their change from baseline will be summarized by treatment group and cohort. Comparisons between treatment groups by cohort on these variables will be carried out where appropriate. Statistical comparisons will be considered descriptive. 95% CIs will be provided along with p values for treatment group comparisons.

Sentinel subjects will be summarized apart for both efficacy and safety.

Pharmacokinetic Analysis:

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

HRQoL and Functional Independence:

For the Health-Related Quality of Life (HRQoL) and functional independence assessments, individual items, domain, and summary scores generated over the course of the study will be evaluated with descriptive statistical measures (mean, standard deviation, minimum, median, and maximum) as well as displayed visually.

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Abbreviations

°C	degree Celsius
ACE	angiotensin-converting enzyme
Ach	Fgfr3G380R achondroplasia mouse model
ACH	achondroplasia
ADR	adverse drug reaction
AE	adverse event
AGV	annualized growth velocity
ALT	alanine aminotransaminase
ANP	atrial natriuretic peptide
AP	anterior-posterior
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMC	bone mineral content
BMD	bone mineral density
BNP	B-type Natriuretic Peptide
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
C_{max}	maximum observed plasma concentration
CBCL	Child Behavior Checklist
CMC	cervicomedullary compression
CNP	C-type natriuretic peptide
CNP53	C-type natriuretic peptide (53 amino acids in length)
CPAP	continuous positive airway pressure
CRA	clinical research associate
CTCAE	Common Terminology Criteria for Adverse Events
CTX-II	C-terminal telopeptide of cross-linked collagen type II
CV	cardiovascular
CV%	coefficient of variation
DCF	data clarification form
DMC	data monitoring committee
DXA	dual X-ray absorptiometry
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
EOSI	events of special interest
ERK	extracellular signal-regulated kinase
EU	European Union
FDA	Food and Drug Administration
FGF	fibroblast growth factor

G380R	substitution in the transmembrane domain of the FGFR3 receptor at position 380
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICH E6 [R2]	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	Independent ethics committee
IgE	immunoglobulin E
IND	Investigational New Drug (application)
IP	investigational product
IRB	institutional review board
ITQOL	Infant Toddler Quality of Life questionnaire
IXRS	Interactive Voice/Web Response System
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond
NAb	neutralizing antibodies
NEP	neutral endopeptidase
NP	natriuretic peptide
NPR-B	natriuretic peptide receptor type B
PI	Principal Investigator
PK	pharmacokinetics
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
REB	research ethics board
rhCNP	recombinant C-type natriuretic peptide
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOI	Statement of Investigator Form
$t_{1/2}$	elimination half-life
TAb	total antibody
TAF	human transcription factor
T_{max}	time to reach C_{max}
ULN	upper limit of normal
US	United States

Wee-FIM	Functional independence measure for children
WFI	water for injection
µg/kg	microgram/kilogram

Definition of Terms:

Investigational Product (IP):

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6] (R2)]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated for subjects who do not speak the local language at 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/IEC/REB confirming unconditional approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the Investigator and copies are received at BioMarin or its designee. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the study are made to the IRB/IEC/REB and BioMarin by the Investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

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

This study will be conducted in accordance with the following:

- European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, for studies conducted within any European country
- 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) or E6(R2) (ICH E6R2) if adopted
- The ethical principles established by the Declaration of Helsinki

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

5.3 Subject Information and Informed Consent

A properly written and executed informed consent form (ICF), in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, 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/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF (minor assent form and parental ICF for studies involving minors), and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

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 Statement of Investigator (SOI) form. A US Food and Drug Administration (FDA) Form FDA 1572 serves as an acceptable SOI form. If Form FDA 1572 may not be used in a particular region, the Investigator must provide a fully executed SOI on the form provided by the Sponsor. All Investigators and Sub-Investigators must be listed on Form FDA 1672 or its equivalent SOI. Financial Disclosure Forms must also be completed for all Investigators and Sub-Investigators listed on the Form FDA 1572 or SOI who will be directly involved in the treatment or evaluation of subjects in this study.

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

In multicenter studies, 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.

7 INTRODUCTION

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

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

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

ACH is caused by a gain-of-function mutation in fibroblast growth factor (FGF)R3, a negative regulator of chondrocyte proliferation and differentiation. The most common mutation (98%) in ACH patients is a G380R substitution in the transmembrane domain of FGFR3 (at position 380). The majority of new cases (80%) originate from parents with normal stature.

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

CNP is a member of the natriuretic peptide (NP) family that includes Atrial Natriuretic Peptide (ANP) and B-type Natriuretic Peptide (BNP). These peptides are structurally related but are distinct paracrine/autocrine (CNP) or endocrine (ANP and BNP) factors that regulate

the cardiovascular (CV), skeletal, nervous, reproductive and other systems. Synthetic analogs of ANP (anaritide and carperitide) and BNP (nesiritide) have been investigated as potential therapies for the treatment of decompensated heart failure and cardiovascular-related diseases.

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

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

7.1 Nonclinical Studies

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

BMN 111-related adverse findings in nonclinical species (mice, rats, cynomolgus monkeys) were limited to the known mechanism of action of CNP on the growth plate and vasculature. Reversible subcutaneous injection site reactions were reported, including injection site discoloration and microscopic findings of perivascular mononuclear cell infiltrates that were seen with slightly higher incidence and severity in BMN 111-treated rats and monkeys compared to the vehicle control. Adverse skeletal changes associated with exaggerated growth were seen in normal nonclinical species with open growth plates, and were dose-, exposure- and time-dependent. Decreases in blood pressure and compensatory increases in heart rate were detected in monkeys across multiple studies, with overt CV-related clinical signs observed in some animals at doses $\geq$ 236 µg/kg. These overt clinical signs consisted of transient, short and repeated bouts of sternal or lateral recumbency and/or reduced motor

activity, typically within 1-hour post-dose administration. Additional detailed information about nonclinical studies of BMN 111 is provided in the current version of the Investigator's Brochure supplied by BioMarin.

7.2 Previous Clinical Studies

7.2.1 Study 111-101

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

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

The PK parameters for BMN 111 were obtained from Part 1 of the study and from the first dose on Day 1 of the multiple dose study in Part 2. The results demonstrate that BMN 111 was rapidly absorbed in human, reaching a mean time to peak concentration (T_{max}) between 15-26 minutes. After reaching maximal plasma concentrations, BMN 111 levels rapidly declined, with a $t_{1/2}$ of 40-55 minutes. Mean plasma concentration-time profiles indicate that exposure increased with dose from 2.5 to 15 µg/kg. The corresponding increases in plasma C_{max} and area under the curve (AUC) exposure parameters were greater than dose proportional. The increase in C_{max} with dose was linear over the dose range evaluated. In Part 2, with multiple dosing at 5 µg/kg for 10 days, the plasma concentration-time curves obtained on each of the three sampling days were nearly superimposable. Comparison of PK

exposure parameters for AUC and C_{max} indicate that C_{max} is unchanged and AUC is increased slightly by +33% over Day 1. Overall, the results indicate that changes in BMN 111 exposure are minimal with repeat dosing out to 10 days.

7.3 Ongoing Clinical Studies

7.3.1 Study 111-901

Study 111-901 is a multicenter, multinational study to collect serial growth measurements on pediatric subjects with ACH who are being considered for subsequent enrollment in future studies sponsored by BioMarin. To obtain accurate baseline measurements, at least 6 months of growth data are collected for Cohorts 1 and 2; and at least 3 months of data for Cohort 3.

Data gathered from this study are used to characterize baseline growth data in children or infants (defined as children < 2 years of age) who may subsequently be enrolled in future studies sponsored by BioMarin, and may also be used to establish historical control cohort for use in other BioMarin-sponsored studies, when appropriate. For that reason, data related to ACH symptoms, tests, and interventions are collected.

7.3.2 Study 111-202

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

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

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

response was observed in change from baseline AGV at doses ranging from 2.5-15 µg/kg daily.

For longer term follow up data from the 202 study, please refer to the current Investigator Brochure supplied by BioMarin.

7.3.3 Study 111-205

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

7.3.4 Study 111-301

Study 111-301 is an ongoing Phase 3, double-blind, placebo-controlled multicenter study to further characterize and confirm efficacy and safety of BMN 111 at 15 µg/kg in a 58-week study (up to 4 weeks of screening, 52 weeks of treatment, plus an additional 2 weeks of safety follow up). The study assesses the effect of daily BMN 111 administration on change from baseline in AGV, height, and body proportions in subjects treated with BMN 111 compared with control subjects in the placebo group; and further characterizes safety and tolerability of BMN 111 in children with ACH. Additional exploratory endpoints are being examined to determine the effect of BMN 111 on bone physiology and to assess quality of life and daily function of study subjects.

7.3.5 Study 111-302

Study 111-302 is an open-label Phase 3 extension study to further evaluate the efficacy and safety of BMN 111 either until subjects reach near-final adult height (defined as evidence of growth plate closure and < 1.5 cm/yr annualized growth velocity), or for 5 years if near-final adult height (NFAH) occurs prior to the end of the 5-year period. All subjects will receive BMN 111 15 µg/kg. This study will allow for long-term assessment of the effect of daily BMN 111 administration on safety, tolerability, growth velocity, height, and body proportions in subjects who have completed 1 year of placebo or BMN 111 treatment in Study 111-301.

7.4 Study Rationale

BMN 111 is a recombinant CNP analogue that has been engineered to resist degradation by NEP, allowing for a longer half-life.

The pharmacological activity of BMN 111 was explored in two mouse models of ACH, a severe, Fgfr3Y367C/+ (TD) model (Lorget, 2012), and a milder [Ach] /+ (Ach) model. These included studies in 7-day old TD mice given BMN 111 daily by SC administration for up to 20 days and a study in 3 week old Ach mice given BMN 111 daily by SC administration for 5 weeks. Partial or complete reversion of the ACH phenotype was observed in these mouse models after BMN 111 administration. In wild-type mice, and normal rats and monkeys, BMN 111 administration resulted in growth plate expansion and dose-dependent skeletal growth at hemodynamically tolerated dose levels (Wendt, 2015). Additionally, the potential effect of age on BMN 111 PK was evaluated in normal rats aged between 7 days and 12-13 weeks.

Infants and young children with ACH have a high incidence of medical complications and currently there is no approved pharmacological therapy for ACH in the US or EU. The most severe complication, cervicomedullary compression (CMC), occurs in a subset of subjects with ACH due to abnormal endochondral bone growth and narrowing of the foramen magnum (White, 2016). CMC has been linked to serious respiratory and neurological complications including hypotonia, apnea, ataxia, developmental delay, and respiratory arrest associated with sudden death (Mukherjee, 2014). Foramen magnum decompression surgery is currently the only treatment for this condition.

Sleep apnea has also been extensively described in ACH, and sleep-disordered breathing may affect up to 85% of all children with ACH (Ireland, 2012). This is thought to be due to midface hypoplasia, relative adenotonsillar hypertrophy, and potential posterior cranial fossa compression secondary to abnormal endochondral bone growth. Sleep apnea in ACH not only results in the need for surgical intervention, but has also been linked to sudden death in rare cases (Pauli, 1984).

Similarly, the dysregulation of endochondral bone growth in ACH leads to other medical complications which are prevalent in this subject population, such as the following:

- Spinal stenosis, kyphosis, and lordosis (secondary to altered growth plate ossification in the vertebrae and narrowing of the interpedicular distances) (Shirley, 2009)
- Developmental delay of gross motor and ambulatory skills (associated with proximal limb shortening, macrocephaly, and hypotonia) (Ireland, 2010)

- Delayed functional skills and increased need for caregiver assistance (eg, eating, bladder management, bowel management, transfer to chair, climbing stairs) (Ireland, 2011)

Thus, BMN 111 may provide greater benefit when children begin treatment at a younger age, as earlier initiation of treatment allows a longer time window to improve growth and potential to improve medical complications of achondroplasia. This study (111-206) is being conducted to assess safety and the potential benefit of BMN 111 in infants and young children.

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

Human studies to date have also demonstrated that BMN 111 is generally well tolerated at doses that result in improvements in growth velocity approaching that of children of average stature (Section 7.3).

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are age 0 to < 60 months. This 52-week study will enable assessment of BMN 111 safety, tolerability, pharmacodynamics biomarkers, and PK in this population, and also allow for examination of potential impact on efficacy endpoints. Additional exploratory endpoints pertaining to medical complications of ACH will also be evaluated.

7.5 Summary of Overall Risks and Benefits

7.5.1 Summary of Risks from Nonclinical Studies

Individuals in this study will be exposed to a recombinant analogue of human C-type natriuretic peptide (CNP). Based on the results of experimentation in animals, the most relevant potential toxicities relate to the expected pharmacological effects of exogenous CNP administration, including hemodynamic changes, skeletal overgrowth, and injection site reactions. Transient and sporadic decreases in blood pressure and compensating increases in heart rate occurred within the first hour post-dose in cynomolgus monkeys; the effects were mainly asymptomatic with a subset of animals given doses ≥ 236 µg/kg observed with

symptomatic effects consisting of transient, short and repeated bouts of sternal or lateral recumbency and/or reduced motor activity. These hemodynamic effects can be monitored, but have the potential to be an acute dose-limiting factor in patients. Exaggerated appendicular bone responses to the drug included abnormally shaped femoral head, acetabular growth center/plate dysplasia and concomitant articular cartilage degeneration with clinical manifestations of restricted use of hips. Adverse skeletal changes associated with exaggerated growth were dose-, exposure- and time-dependent. Additional detailed information about risks identified in nonclinical studies of BMN 111 is provided in the current version of the Investigator's Brochure supplied by BioMarin.

7.5.2 Summary of Risks from Clinical Studies

7.5.2.1 Study 111-101

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

7.5.2.2 Ongoing Studies

Based on analysis of safety data from ongoing phase 2 and 3 studies, treatment with BMN 111 was generally well tolerated. Injection site reactions were the most common adverse events reported and are considered to be an identified risk. All injection site reactions events have been reported as non-serious, Grade 1 in severity, and transient. Hypotension and hypersensitivity reactions including development of BMN 111 antibodies are potential risks associated with BMN 111 injections. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

7.5.3 Summary of Potential Benefits from Clinical Studies

For children with ACH who will receive BMN 111 as part of Study 111-206, potential benefits may include improvement of AGV rates such that their increase in growth velocity may approach that of children of average stature. Additional potential benefits may include improvement of the disproportionate growth as well as improvement in quality of life, activities of daily living, and medical complications of ACH. For example, improvement in height could have an impact on daily activity performance.

8 STUDY OBJECTIVES

The primary objectives of the study are to:

- Evaluate the safety and tolerability of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate the effect of BMN 111 on change from baseline in length/height Z-score

The secondary objectives of the study are to:

- Evaluate the effect of BMN 111 on change from baseline in AGV throughout the 52 weeks of the study
- Evaluate the effect of BMN 111 on bone morphology/quality by X-ray and dual X-ray absorptiometry (DXA)
- Evaluate the PK of BMN 111 in children age 0 to < 60 months with ACH
- Evaluate hip function
- Evaluate for hip, thigh, or knee pain, or change in gait
- Evaluate the effect of BMN 111 on HRQoL, developmental status, and /functional independence using age-specific QoL and functional independence questionnaires/QOL status (Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III], Activity of Daily Living and Functional Independence Measure (Wee-FIM), Infant Toddler Quality of Life Questionnaire (ITQOL), Child Behavior Checklist (CBCL)
- Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures
- Evaluate the effect of BMN 111 on bone metabolism and BMN 111 pharmacodynamic biomarkers
- Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower body segment ratio
- Evaluate the effect of BMN 111 on sleep apnea
- Evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions
- Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy

The exploratory objectives of the study are to:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH.

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

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

The primary objectives of this study are to assess the safety and tolerability of daily SC BMN 111 administered to infants and young children with ACH, and evaluate the effect of BMN 111 on Z-scores. Subjects will be enrolled into 3 age cohorts based on age at study screening starting with the eldest population. Within Cohorts 1 and 2, subjects will be stratified by age:

- Cohort 1 – children aged ≥ 24 to < 60 months (n ≥ 30 total: 3 sentinel subjects who receive BMN 111, and at least 27 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 24 to < 36 months and ≥ 36 months to < 60 months)
- Cohort 2 – children aged ≥ 6 to < 24 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control), stratified by age (≥ 6 months to < 15 months and ≥ 15 months to < 24 months)
- Cohort 3 – children aged 0 to < 6 months (n ≥ 20 total: 3 sentinel subjects who receive BMN 111, and at least 17 additional subjects randomized 1:1 to treatment or placebo control). Treatment begins at ≥ 3 months to < 6 months after 3 months of observation.

If subjects who enroll in Cohort 3 are not able to begin treatment by < 6 months of age, they will continue in the pretreatment period for another 3 months before enrolling in Cohort 2 to fulfill the pretreatment requirement for Cohort 2.

Sentinel subjects from each cohort will be enrolled, treated with BMN 111, and studied for short-term safety and PK data. No two sentinel subjects will be dosed on the same day for any cohort. After the sentinel data are evaluated, additional recruited subjects will be randomized to receive BMN 111 or placebo SC daily (1:1 ratio) for 52 weeks. At the start of the study, 3 sentinel subjects will be enrolled and monitored in Cohort 1. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 1 (≥ 27 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a data monitoring committee (DMC) review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort (Cohort 2) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 2. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 2 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio). After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the youngest cohort (Cohort 3) will be opened and the 3 sentinel subjects will be enrolled.

The same procedure will be followed for Cohort 3. After all 3 sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety data and Day 1 PK data. Based on PK data and criteria set in the protocol, the dose may be adjusted for the sentinel subjects and the rest of the cohort, and will be the starting dose for the younger cohort sentinel subjects. Upon review of the clinical and PK data, the remainder of Cohort 3 (≥ 17 additional subjects) will be enrolled and randomized to treatment with BMN 111 or placebo (1:1 ratio).

Cohort 3 subjects must have a minimum of 3 months of observation prior to commencement of treatment. These subjects will have the option to enroll in either 111-901 or 111-206.

Additional sentinels may be added to any cohort if needed for additional safety and/or PK assessment.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥ 24 to < 60 months.

Each treated subject will have expanded outpatient safety monitoring for a minimum of 3 days of dosing, during which they will be closely observed and non-invasive hemodynamic monitoring will be conducted for at least 4-8 hours post-dosing. Because younger children may not be able to verbalize complaints of dizziness or lightheadedness that are potentially associated with hypotension, study personnel and caregivers will be trained to recognize the signs of hypotension in this population, which may include tachycardia, pallor, diaphoresis, lethargy, delayed capillary refill, and poor feeding. Appropriate rigorous training will be required for parents and caregivers prior to daily injections at home. Training includes the storage, reconstitution, and administration of BMN 111, as well as documentation/reporting of AEs and vigilance for signs of hypotension.

It is generally expected that after subjects are tolerating the drug well and specified criteria have been met, caregivers will begin administering study drug. Home health care is not required at any point but may be provided if the caregiver is unable or unavailable to administer the study drug. A Home Healthcare nurse will train the caregiver(s) if training has not been completed by the Day 3 visit. A phone call by the study staff member to the caregiver will be required weekly for 6 months and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. If the caregiver cannot be contacted by phone after two attempts, contact can be made via email.

Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in all treatments groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term. For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

A summary of events and assessments are provided by visit in Table 9.1.1 and Table 9.1.2.

For a discussion of efficacy assessments, see Section 9.12.2 and Section 9.12.3; exploratory efficacy assessments, Section 9.12.4; safety assessments, Section 9.12.6; and PK variables, Section 9.12.5. The 111-206 study design is presented in Figure 9.1.1.

Figure 9.1.1: Study Design

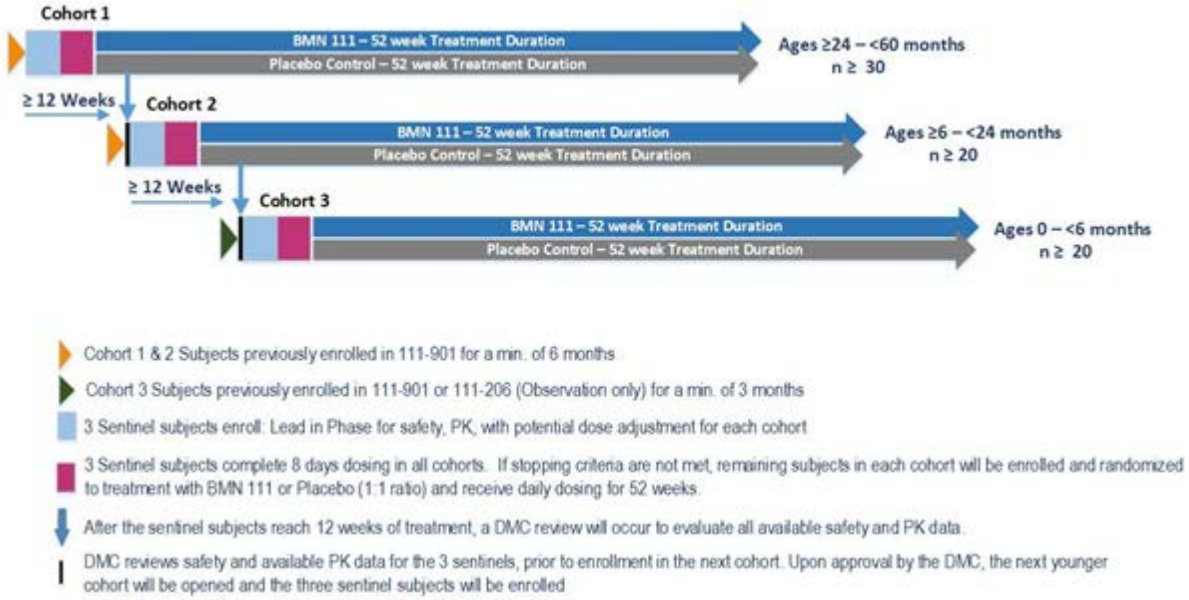


Table 9.1.1: Schedule of Events

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (+7d)[aa]	Early Term Visit
Informed consent	X													
Medical history[c]	X													
Parental height (optional)[d]	X													
Diagnostic genetic testing to confirm achondroplasia (if needed)[e]	X													
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[h]	X	X			X		X	X	X	X	X	X	X	X
Echocardiogram[i]	X												X	X[i]
Anthropometric measurements[j]	X	X					X	X		X	X	X		X[j]
Clinical laboratory assessments (hematology, chemistry, urinalysis)[k]	X				X	X	X		X		X	X		X
Thyroid function tests	X											X		
Vitamin D, 25-hydroxy test	X											X		
Salivary cortisol	X									X		X		X
Serum prolactin	X									X		X		X
Plasma PK and cGMP assessments[l]		X						X		X	X	X		
Anti-BMN 111 immunogenicity[m]		X				X		X		X		X		X

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (+7d)[aa]	Early Term Visit
Genomic biomarkers (optional)[n]	X													
Bone metabolism blood biomarkers[n]	X				X		X		X		X			X
Bone metabolism urine biomarkers[o]		X	X	X		X		X		X	X	X		X
BMN 111 PD urine biomarkers[o]		X	X	X		X		X		X	X	X		X
Urine chemistry[o]		X	X	X		X		X		X	X	X		X
Hip monitoring[p]										X		X		X
MRI brain/skull[q]	X											X		X
Sleep study[r]	X											X		X
Clinical outcome assessment: Bayley-III	X									X		X		X
Clinical outcome assessment: Wee-FIM[s]	X									X		X		X
Clinical outcome assessment: ITQOL[s]	X									X		X		X
Safety assessment: CBCL[s]	X									X		X		X
DXA (BMD and BMC) of whole body [less head], spine)[t]	X											X		X[t]
AP and lateral X-rays of spine[u]	X											X		X[u]
AP X-rays of lower extremities[u]	X											X		X[u]
Clinical photographs (optional)[v]	X											X		X

Procedure[a]	Screening/ Baseline Day -30 to Day -1[b]	Day 1	Day 2	Day 3	Day 8 (±1d)	Week 3 (±7d)	Week 6 (±7d)	Week 13 (±7d)	Week 20 (±7d)	Week 26 (±7d)	Week 39 (±7d)	Week 52 (±7d)	Week 56 Safety Follow-Up (+7d)[aa]	Early Term Visit
Capture concomitant procedures/interventions/ surgeries		All visits											X	X
BMN 111 or placebo administration[w]		All visits												
BMN 111 or placebo accountability		All visits												X
Adverse events[x]		All visits											X	X
Concomitant medications[y]	X	All visits											X	X
Phone call[z]		Weekly calls for 6 months and then every 2 weeks for the remainder of the study												
Home health visit		Home health visit is not required at any point but may be provided if the caregiver is unable or unavailable to administer the study drug.												

[a] Clinic visits (except Days 1, 2, 3, and 8) have a ± 7-day window. Anthropometric measurement and imaging assessments can be conducted either pre-dose or post-dose.

[b] If the 111-901 visit at which the subject enters Study 111-206 and the 111-206 Screening visit are on the same day, the procedures common to both visits will be performed one time only. All blood tests at Screening visit should be obtained between Day −30 and Day −14.

[c] 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.

[d] Standing height of the participant's biological parents may 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, the parent can provide their stated height instead if consent has been given.

[e] If subjects had previous genetic testing, subjects must have a lab certification documenting the specific mutation required for the 111-206 study, including the identification of FGFR3 mutation (G346E, G375C, G380R, or "other").

[f] Complete physical exam includes 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.

[g] 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, BP, and respiratory rate.

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

1. Vital sign measurements are taken once per time point, preferably in a sitting or supine position, after at least 5 minutes of rest.
2. Heart rate, blood pressure, and respiratory rate should be taken and recorded at each indicated time point.
3. When blood samples and vital sign assessments are scheduled at the same time or within the same time window, vital signs should be measured before blood samples are drawn.
4. If a vital sign measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and wait several minutes before measuring vital signs.
5. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
6. If a subject has a hypotensive event, or signs potentially consistent with hypotension, or a decrease of 20 mm Hg systolic BP or more from baseline (defined by pre-dose vitals collected that day), vital signs should be measured and recorded approximately every 15 minutes (± 5 minutes) for the first hour and every 30 minutes (± 5 minutes) thereafter until the BP returns to baseline (or within the normal range for this subject as defined by PI) and signs (if present) resolve.
7. If the decision is made to adjust the dose, vital signs will be obtained for at least 4 hr following the first dose at the adjusted dose level, similar to the Day 3, 8 schedule.
8. If a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1, 2 schedule.

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

[i] Echocardiogram is obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination.

[j] Growth measures may be collected in triplicate 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 length, standing height (if able to stand unsupported), crown-to-rump length, head circumference, upper and lower arm and leg, and arm span. Measurements not taken in the midsagittal plane should be taken on the right side of the body if possible and should always be taken on the same side of the body throughout the study. Anthropometric measurements will be taken at the ETV only if subject discontinues after Week 6 and if > 2 weeks have elapsed since the previous assessment.

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

[l] Plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes. Samples with volume remaining after pharmacokinetic assessment will be used for cGMP pharmacodynamics assessment. NOTE: In the event of interruption of study drug administration for a sentinel patient on Day 1 when PK samples are scheduled, the collection of PK samples should be delayed until the subsequent day and only performed after successful administration of study drug has been completed in a single injection.

[m] Antibodies: Total anti-BMN 111 (TAb), TAb cross-reacting with endogenous natriuretic peptides, and neutralizing antibody (NAb) samples (serum) will be drawn pre-dose at each time point listed on the SOE. TAb cross-reacting with endogenous natriuretic peptides and NAb testing will be performed only on baseline and TAb positive samples from subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg. Drug-specific IgE will be drawn pre-dose on Day 1 for subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg to stay within the limits of permitted blood volume collections in infants. Total immunoglobulin E (IgE) and drug-specific IgE will be drawn in the event of Grade 3 hypersensitivity adverse event) or at Investigator or Sponsor discretion. If such an event occurs, the drug-specific IgE sample should be drawn at least 8 hours after the event start time or 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 an unscheduled safety visit.

[n] For optional genomic biomarkers, if the sample is not collected on Day 1, it may be drawn at any time during the study. The sample will be used for exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signalling. Bone metabolism blood biomarkers will be waived at screening for subjects weighing < 7.0 kg to limit the blood volume on the smallest subjects at this visit. Serum samples for bone metabolism biomarkers will be collected pre-dose on the indicated visits. Bone metabolism blood biomarkers include bone-specific alkaline phosphatase and collagen type X.

[o] Urine biomarkers and urine chemistry (urine creatinine test) should be obtained pre- and post-dose (approximately 2-4 hours after study drug administration) for subjects when possible at the indicated visits. The time of collection will be recorded. Urine biomarkers include cGMP and C-terminal telopeptide of cross-linked collagen type II (CTX-II).

[p] 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. Adverse changes from baseline will trigger further evaluation.

[q] MRI is obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC). Efforts to obtain a satisfactory image can be discontinued after 3 unsuccessful attempts.

[r] If sleep study is uninterpretable, subject may need to repeat assessment. Obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC).

[s] Wee-FIM is waived for children < 6 months old; CBCL is waived for children < 18 months old. ITQOL and CBCL should be performed before any other assessments during the study visit.

[t] Efforts to obtain a satisfactory image can be discontinued after 3 unsuccessful attempts. DXA will be obtained at ETV only if subject discontinues after 9 months to reduce unnecessary radiation exposure (unless additional scans are recommended by investigator, BioMarin, or DMC).

[u] AP and lateral lumbar spine, and AP lower extremities are obtained at the early termination visit only if the previous assessment was done more than 9 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC). Obtained at ETV only if subject discontinues after 9 months to reduce unnecessary radiation exposure (unless additional X-rays are recommended by investigator, BioMarin, or DMC).

[v] To document the physical and phenotypic findings of achondroplasia with and without treatment with study drug, clinical photography of the full body, face, spine, and extremities will be conducted. This assessment is optional. If the parents/caregivers decline clinical photography, the assessment will be waived for the duration of the study.

[w] The injection site should be rotated as described in the BMN-111 Injection Guide. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic. If interruption of study drug injection occurs, the remainder of the assigned dose should be administered immediately (and no later than within 5 minutes) in a different location. The same syringe should be used and newly reconstituted investigational drug should be used to draw the remainder of the dose.

[x] 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.

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

[z] During the call study staff will ask the caregiver about correct administration procedures, record adverse events (AEs), record concomitant medications, and answer questions.

[aa] The 4-week safety follow up visit will be waived for subjects who enter another BMN 111 study or registry within the 4-week period following last dose of study drug.

Table 9.1.2: Schedule of Events Observational Period for Cohort 3 (infants between birth and < 3 months old)

Assessments	Screening[a]	Day 1[a] (Month 0)	3 Months (± 10 days)
Informed consent	X		
Medical history, including growth history and ACH related history	X		
Concomitant medications	X	X	X
Physical examination[b]	X		
Vital signs[c]	X	X	X
Anthropometric measurements[d]		X	X
Vitamin D, 25-hydroxy[e]	X		X
Alkaline phosphatase[e]	X		X
Bone metabolism blood biomarkers	X		X
Bone metabolism urine biomarkers	X		X
Genomic biomarkers (optional)[f]		X	
Weight		X	X
Body mass index (calculated)		X	X
Clinical outcome assessment: Bayley-III[g]		X	
Clinical outcome assessment: ITQOL[g]		X	
Capture concomitant procedures/interventions/surgeries		X	X
Adverse events[h]	X	X	X

[a] Screening and Day 1 (Month 0) assessments may be performed on the same calendar day at the discretion of the investigator. If Screening and Day 1 (Month 0) are done on the same day, vital signs are taken only once. Please refer to eCRF Completion Instructions.

[b] A complete physical examination will be performed at Screening. Complete physical exam includes 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.

[c] Vital signs will be measured with appropriate blood pressure cuffs for achondroplasia children following detailed instructions in Study Reference Manual. At screening, blood pressure should be taken with subject in a supine position, after the subject has been resting for at least 5 minutes. At all other visits, blood pressure should be taken one time after at least 5 minutes of rest, with subject in a supine position. Heart rate should be taken at each time point that blood pressure is measured. Left brachial arm should be the first method of assessment considered, and the same site should be used for blood pressure measurement in each subject throughout the study. The method and site of blood pressure measurement will be recorded and should be utilized consistently throughout the remainder of the study.

[d] Growth parameters (anthropometric measurements) may include but are not limited to height, standing height, sitting or supine height, weight, upper and lower arm and leg length, and arm span. Body proportion measurements may include but are not limited to upper:lower body segment ratio, upper arm:forearm length ratio, upper leg:lower leg length ratio, and arm span:standing height ratio. Refer to the Anthropometric Measurement Guidelines for specific instructions regarding the collection of growth measurements. All age-appropriate physical measurements will be collected at approximately the same time each visit (± 2 hours) by a trained study staff member; every effort will be made to have the measurements collected by the same study staff member, if possible, throughout the study. Each measurement will be taken in triplicate (excluding weight, taken once).

[e] Vitamin D (25-hydroxy) and alkaline phosphatase will be measured during Screening and at the 3-month visit.

[f] If sample is not collected at Day 1, it may be drawn at any time during the study. The sample will be used for exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signaling.

[g] Bayley-III is waived for subjects < 1 month old; ITQOL is waived for subjects < 2 months old.

[h] AEs will be collected at screening. For subjects enrolled in Cohort 3 (0 to <6 months old), the collection period for all AEs begins after informed consent is obtained.

9.1.1 Dose Adjustments

Analysis of available PK data from studies 111-101 and 111-202 indicated that differences in subject body weight did not directly translate to differences in total body clearance of BMN 111. The same weight-based dose in the pediatric population of Study 111-202 (5-12 years old) yielded lower exposure (C_{max} and AUC) than that characterized in the adult population of Study 111-101. Therefore, the same weight-based dose in the young pediatric population in this study may yield exposure less than the target exposure range characterized to be safe and effective in Study 111-202 at the 15 µg/kg dose. Since this is the first experience with BMN 111 in this young pediatric population, it is also possible the exposure at 15 µg/kg could be greater than the target exposure range, and dose adjustment may be warranted. Thus, an option for adjustment of the weight-based dose is provided to ensure that the appropriate target exposure for safety and efficacy is reached for the young subjects in this study.

The need for dose adjustment will be evaluated as follows: three sentinel subjects in Cohort 1 will receive an initial dose of 15 µg/kg. After all three sentinel subjects reach Day 8, the Sponsor will review and evaluate all available safety and PK data (at minimum). If the criteria for dose adjustment are met, the three sentinel subjects will be started on the new adjusted dose at their next scheduled visit, and vital signs will be obtained for at least 4 hours post-dose.

The remainder of the subjects in the age cohort will also be enrolled starting at the new adjusted dose. After the third sentinel subject reaches Week 12 post dose adjustment, a DMC review will occur to evaluate all safety and PK data and, upon endorsement, the three sentinel subjects from the next younger cohort will be enrolled starting at the new adjusted dose. The three sentinel subjects for the second and third cohorts will be evaluated similarly to the sentinel subjects in the first cohort for potential dose adjustment.

As subjects age on study, they will be administered the dose determined to be appropriate for their current age. For example, if a subject enrolls into Cohort 2 at age 20 months, they will receive the recommended dose for subjects aged ≥ 6 to < 24 months until they turn 24 months in age. When they turn 24 months in age, they will begin to receive the recommended dose for subjects aged ≥ 24 to < 60 months.

Criteria for Dose Adjustment

The criteria for dose adjustment are based on obtaining equivalent exposure characterized to be safe and effective with the 15 µg/kg dose in Study 111-202 in each of the age cohorts evaluated in this study. BMN 111 dose may be adjusted if the mean observed $AUC_{0\text{-}120}$ from

sentinel subjects is less than the 25th percentile for $AUC_{0\text{-}120}$ in Cohort 3 (15 µg/kg) of Study 111-202 or greater than the 75th percentile in Cohort 3 of Study 111-202. If these criteria are met, an allometric scaling coefficient, α, for BMN 111 clearance by subject body weight will be determined using a population PK modelling approach and available data from this study and Studies 111-202 and 111-101. The recommended adjusted dose will be determined using the following expression:

$$Dose_{ch} = Dose_{ref}\left(\frac{WT_{ch}}{WT_{ref}}\right)^{\alpha}$$

where WT_{ref} and $Dose_{ref}$ are the typical (i.e., median) subject body weight and total dose, respectively, at the 15 µg/kg dose level in Cohort 3 of Study 111-202, and WT_{ch} is the anticipated median weight in the age cohort being studied. As such, the recommended adjusted dose will target the median $AUC_{0\text{-}120}$ observed at the 15 µg/kg dose level of Study 111-202. The recommended adjusted dose, $Dose_{ch}$, will be normalized by WT_{ch}, to provide the recommended adjusted weight-based dose. The following rules will be used for dose adjustment:

- A maximum of a 2-fold increase in dose/kg will be permitted between dose adjustments regardless of exposure.
- The total dose will not exceed the highest total dose administered in Study 111-202.

9.1.2 Stopping Criteria

Individual Subject Stopping Criteria

For individual subjects treated with BMN 111, DMC will be informed if any of the following individual subject stopping criteria should occur. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the individual subject will be considered.

- Any treatment-emergent adverse event (AE) assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (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

- Clinically significant finding or arrhythmia on electrocardiogram (ECG) that indicates abnormal cardiac function or conduction or prolongation of QTc-F > 500 msec
- Clinically significant new or worsening signs of cervicomedullary compression as determined by the Investigator and in consultation with Sponsor medical monitor and neurosurgical specialist (if needed)
- Adverse findings on clinical hip exam or hip imaging assessments that are determined to be clinically significant as determined by the Investigator and in consultation with Sponsor Medical Monitor and orthopedic specialist (if needed)

If the subject meets any stopping criterion, 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
- Permanent treatment discontinuation (with an option of ongoing assessment in the study)

Cohort Stopping Criteria

For each cohort, a DMC review will be conducted if any of the following cohort stopping criteria occur in subjects treated with BMN 111. Temporary dosing suspension, permanent discontinuation of dosing, or dose reduction for the cohort(s) will be considered and the impact on all other age cohorts will be assessed.

- Any treatment-emergent AE assessed as at least Grade 4 by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have a treatment-emergent AE of at least Grade 3 assessed as related to study drug by the Investigator and/or Sponsor Medical Monitor
- Any two subjects have two treatment-emergent Grade 2 symptomatic hypotension events within 7 days (non-urgent medical intervention indicated) or any two subjects cohort have a Grade 3 hypotensive event (urgent medical intervention or hospitalization indicated) assessed by the Investigator and/or Sponsor's Medical Monitor
- Any two subjects have a clinically significant finding or arrhythmia on ECG that indicates abnormal cardiac function or conduction or prolongation of QTc-F >500 msec

- Any two subjects have adverse 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)

9.2 Discussion of Study Design, Including Choice of Control Group

Study 111-206 is a Phase 2 randomized, double-blind, placebo-controlled clinical trial of BMN 111 in infants and younger children with a diagnosis of ACH who are age 0 to < 60 months. Identification of efficacy at this age range is congruent with mechanism of action of BMN 111, because BMN 111 is expected to act at open epiphyseal growth plates. Therefore, to have a potential therapeutic benefit for subjects with ACH, specifically for the foramen magnum and spine, treatment is expected to be required prior to growth plate closure.

In terms of the study design, a randomized double-blind placebo control will be used to mitigate the risk of selection bias and any potential bias in data collection and study conduct. Additionally, this design provides a framework for interpretation of any endpoints with a subjective component, e.g. health-related quality of life (HRQoL) and activities of daily living (ADL) questionnaires and any subjective assessment of safety.

9.3 Selection of Study Population

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

Additional criteria for participation in the study are provided in Sections 9.3.1 and 9.3.2.

9.3.1 Inclusion Criteria

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

1. Diagnosis of ACH, confirmed by genetic testing. If subjects had previous genetic testing, subjects must have a lab report from a certified laboratory with the study specific mutation documented.
2. Age 0 to < 60 months, at study entry (Day 1)
3. Cohort 1 and 2 subjects must have at least a 6-month period of pretreatment growth assessment in Study 111 901 immediately before screening, and have one documented measurement of height/body length a minimum of 6 months prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrollment in Study 111-901 or (2) via enrollment in this Study 111 206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment.

4. Parent(s) or guardian(s) (and the subjects themselves, if required by local regulations or ethics committee) 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
5. Willing and able to perform all study procedures as physically possible
6. Parent(s) or caregiver(s) are willing to administer daily injections to the subjects and complete the required training

9.3.2 Exclusion Criteria

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

1. Have hypochondroplasia or short-stature condition other than achondroplasia (e.g., trisomy 21, pseudoachondroplasia, etc.)
2. Subject weighs < 5.0 kg (Cohort 1 and 2) or < 4.0 kg (Cohort 3)
3. Have any of the following:
    - Hypothyroidism or hyperthyroidism
    - Insulin-requiring diabetes mellitus
    - Autoimmune inflammatory disease (including celiac disease, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, etc.)
    - Inflammatory bowel disease
    - Autonomic neuropathy
4. Have a history of any of the following:
    - Renal insufficiency defined as serum creatinine > 2 mg/dL
    - Chronic anemia or Hgb < 10.0 g/dL (based on screening clinical laboratory testing)
    - Baseline systolic blood pressure (BP) below age and gender specified normal range or recurrent symptomatic hypotension (defined as episodes of low BP generally accompanied by symptoms e.g., dizziness, fainting) or recurrent symptomatic orthostatic hypotension
    - Cardiac or vascular disease, including the following
        - Cardiac dysfunction (abnormal echocardiogram determined to be clinically significant by principal investigator [PI] and medical monitor) at Screening Visit
        - Hypertrophic cardiomyopathy
        - Pulmonary hypertension
        - Congenital heart disease with ongoing cardiac dysfunction
        - Cerebrovascular disease
        - Aortic insufficiency or other clinically significant valvular dysfunction
        - Clinically significant atrial or ventricular arrhythmias

6. Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-F > 450 msec on screening ECG
7. Have evidence of cervicomedullary compression (CMC) likely to require surgical intervention within 60 days of Screening as determined by the Investigator and informed by the following assessments:
   - Physical exam (e.g., neurologic findings of clonus, opisthotonus, exaggerated reflexes, dilated facial veins)
   - Polysomnography (e.g., severe central sleep apnea)
   - MRI indicating presence of severe CMC or spinal cord damage
8. Have an unstable medical condition likely to require surgical intervention in the next 6 months, or planned spine or long-bone surgery (i.e., surgery involving significant disruption of bone cortex) during the study period
9. Have documented uncorrected Vitamin D deficiency: 25(OH)D ≤ 15 ng/mL (37.5 nmol/L)
10. Require any other investigational product prior to completion of the study period
11. Have received another investigational product or investigational medical device within 30 days prior to the Screening visit
12. Have used any other investigational product or investigational medical device for the treatment of achondroplasia or short stature at any time
13. Require current chronic therapy with antihypertensive medication or any medication that, in the investigator's judgment, may compromise the safety or ability of the subject to participate in this clinical study (Table 9.3.5.1)
14. Have been treated with growth hormone, insulin-like growth factor 1 (IGF-1), or anabolic steroids in the 6 months prior to screening, or long-term treatment (> 3 months) at any time
15. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) in the 12 months prior to screening
16. Have ever had cervicomedullary decompression surgery (Cohorts 2 and 3 only), spine or long-bone surgery (i.e., surgery involving disruption of bone cortex) or have ever had bone-related surgery with chronic complications
    NOTE: Subjects with prior cervicomedullary decompression may be allowed into Cohort 1 only after discussion and agreement with Medical Monitor.
17. Have ever had limb-lengthening surgery or plan to have limb-lengthening surgery during the study period
18. Have had a fracture of the long bones or spine within 6 months prior to screening

19. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin greater than upper limit of normal (ULN) at screening (except for subjects with a known history of Gilberts or newborns entering screening in Cohort 3)
20. Have evidence of severe untreated sleep apnea; or have newly initiated sleep apnea treatment (eg, continuous positive airway pressure [CPAP] or sleep apnea-mitigating surgery) in the 2 months prior to screening
21. Have current malignancy, history of malignancy, or currently under work-up for suspected malignancy
22. Have known hypersensitivity to BMN 111 or its excipients
23. Have a history of hip surgery or severe hip dysplasia
24. Have a history of clinically significant hip injury in the 30 days prior to screening
25. Have a history of slipped capital femoral epiphysis or avascular necrosis of the femoral head
26. Have abnormal findings on baseline clinical hip exam or imaging assessments that are determined to be clinically significant as determined by the Investigator
27. 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
28. Have any concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, for any reason

9.3.3 Inclusion Criteria for Cohort 3 Observation Period

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

1. Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research-related procedure. Also, willing and able to provide written assent (if applicable) after the nature of the study has been explained and prior to performance of any research-related procedure.
2. Birth to ≤ 3 months of age at study entry.
3. Have ACH, documented by genetic testing
4. Are willing and able to perform all study procedures as physically possible

After completing the observation period, subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug.

9.3.4 Exclusion Criteria for Cohort 3 Observation Period

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 disorders:
   - Hypothyroidism
   - Insulin-requiring diabetes mellitus
   - Autoimmune inflammatory disease (including celiac disease, lupus (SLE), juvenile dermatomyositis, scleroderma, and others)
   - Inflammatory bowel disease
   - Autonomic neuropathy
3. Have an unstable clinical condition likely to lead to intervention during the course of the study, including progressive cervical medullary compression
4. Have a history of any of the following:
   - Renal insufficiency
   - Anemia
5. Have a history of cardiac or vascular disease, including the following:
   - Cardiac dysfunction
   - Hypertrophic cardiomyopathy
   - Congenital heart disease
   - Cerebrovascular disease, aortic insufficiency
   - Clinically significant atrial or ventricular arrhythmias
6. Current treatment 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, drugs known to alter renal function that is expected to continue for the duration of the study
7. Have had regular long-term treatment (> 1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable) in the previous 3 months
8. Concomitant medication that prolongs the QT/QTc interval within 14 days or 5 half-lives, whichever is longer, before the Screening visit
9. Have used any other investigational product or investigational medical device for the treatment of ACH or short stature
10. Planned or expected bone-related surgery (ie. surgery involving disruption of bone cortex), during the study period.
11. Planned or expected to have limb-lengthening surgery during the study period.
12. Have any condition that, in the view of the Investigator, places the subject at high risk of poor compliance with the visit schedule or of not completing the study.

13. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation

After completing the observation period, subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug.

9.3.5 Current Chronic Therapy with Restricted Medications

Table 9.3.5.1 lists the medications that are restricted in Study 111-206.

Table 9.3.5.1: Current Chronic Therapy with Restricted Medications

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

9.3.6 Removal of Subjects from Treatment or Assessment

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

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

1. Subject experiences a serious or intolerable AE due to BMN 111 as determined by the subject, investigator, or sponsor
2. Subject requires medication or medical procedure prohibited by the protocol
3. Subject does not adhere to study requirements specified in the protocol
4. Subject is lost to follow-up

If a subject fails to return for scheduled visits, a 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 contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as HIPAA in the US, from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

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

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

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

9.3.7 Subject Identification

Each subject will be assigned a unique subject identifier. This unique identifier will be on all eCRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

9.3.8 Duration of Subject Participation

Duration of the study is 52 weeks of treatment with a safety follow up at Week 56. Following completion of the study, subjects in both treatments groups may be eligible to receive BMN 111 in an open-label extension study, to assess safety and efficacy of BMN 111 over the longer term. For subjects enrolling into the extension study, safety follow up visit at Week 56 will be waived.

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

Follow-up assessments and procedures should be performed as outlined in the Study 111-206 Schedule of Events (Table 9.1.1 and Table 9.1.2).

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

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

9.4 Treatments

9.4.1 Treatments Administered

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

Sentinel subjects will receive BMN 111 at a daily dose of 15 µg/kg (subject to adjustment per protocol). Subjects will be randomized to BMN 111 or placebo at a daily dose of 15 µg/kg (subject to adjustment per protocol) for the duration of the study. The normal dosing schedule is a single daily subcutaneous injection given 7 days a week.

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

9.4.1.1 Study Drug Administration

During the study, BMN 111 or placebo will be administered as a single 15 µg/kg SC injection given daily at approximately the same time each day whenever possible. The same injection site should not be used 2 days in a row, and sites should be rotated. Study drug should be administered at age-appropriate locations (upper thigh, upper back of arm, abdomen or buttocks). Determination of appropriate injection sites will be left to the discretion of the investigator. Doses may be administered in any of the common SC areas (upper arm, thigh, abdomen, buttocks).

9.4.1.1.1 Observation Period

Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic. Instructions for home administration of BMN 111 or placebo for subjects who qualify for parent/caregiver administration are provided in the Study Drug Injection Guide and Injection media.

9.4.2 Identity of BMN 111

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

PGQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC

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

9.4.2.1 Product Characteristics and Labeling

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

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

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

9.4.3 Storage

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

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

9.4.4 Directions for Administration

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

The injection will be administered as a daily dose of BMN 111 15 µg/kg or placebo given as a single subcutaneous injection. The dose should be given at approximately the same time every day whenever possible. Following administration of each dose at clinic visits, subjects should be observed for 8 hours after the injection on Days 1 and 2; 4 hours on Days 3 and 8; and 1 hour on subsequent dosing visits. Subjects should be observed for 30 minutes after every injection that is not administered at the clinic. Subjects should have adequate food intake prior to dosing. All subjects should have been well hydrated and fed in the hour prior to administration of BMN 111 or placebo.

Caregivers will administer BMN 111 or placebo at home once approved by the investigator and adequate training is demonstrated. Instructions on how to complete and document the training can be found in the Study Reference Manual.

A caregiver will be eligible to administer BMN 111 or placebo if he or she meets all of the following criteria:

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

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

The caregiver will be provided with a paper or electronic study diary and will be asked to record daily dosing information, changes in health status, medications and injection sites used, date and time of the injection, and injection site reactions, if any.

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

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized using an interactive voice/response system (IXRS) in a 1:1 ratio, i.e., injection with placebo:15 µg/kg of BMN 111. An independent third-party vendor will develop the randomization schedule so that BioMarin and site personnel are blinded to treatment assignments. NOTE: In Japan, subjects are randomized separately within each cohort.

9.4.6 Selection of Dose and Dosing Schedule Used in the Study

Study 111-202, the second clinical trial in humans and the first in children with ACH, is an ongoing Phase 2, open-label, sequential-cohort, dose-escalation study that assesses daily SC BMN 111 in pediatric subjects with ACH aged 5-14 years with doses ranging from 2.5 µg/kg to 30 µg/kg.

Analysis of safety data from the 6-month initial phase of Study 111-202 showed that treatment with BMN 111 for 6 months at the doses of 2.5, 7.5, 15, and 30 µg/kg was generally well tolerated. The most common AEs across all cohorts were injection site reactions, asymptomatic hypotension, headache, and nasopharyngitis. Based on previous experience of the ongoing Phase 2 clinical trial, including the 24-month data cut at 15 µg/kg, injection site reactions have been identified as risks associated with BMN 111 injections. For a detailed summary of risks, please refer to the current version of the Investigator's Brochure supplied by BioMarin.

Analysis of efficacy data from the 6-month initial phase of Study 111-202 showed that subjects treated with BMN 111 for 6 months at doses ranging from 2.5 to 15 µg/kg daily had a dose-dependent improvement in AGV, with ~50% improvement in AGV seen at the 15 µg/kg dose. The data from Cohort 4 (30 µg/kg) show an apparent greater than dose-proportional increase in BMN 111 plasma exposure (C_{max} and AUC_{0-t}), 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).

Efficacy/toxicity studies have been conducted in neonatal and very young animals (7-day postpartum mouse and rat) in both a disease (TD mouse) and non-disease (rat) model. Given that this is the first study in infants and young children, an age-based cohort study design is used to assess safety and PK in young children (Cohort 1, ≥ 24 to < 60 months) prior to dosing toddlers (Cohort 2, ≥ 6 to < 24 months) and infants (Cohort 3, 0 to < 6 months). PK will be monitored and evaluated; Day 1 PK data from the sentinel subjects will inform dose selection modification for the sentinel subjects and for the rest of the cohort to target the observed exposure of the 15-µg/kg dose group in Study 111-202.

Safety, efficacy and PK data from Study 111-202, a Phase 2 study in children with ACH, where a dose of 15 µg/kg has been and continues to be studied, are expected to be the most relevant, and translatable to this study (111-206).

9.4.6.1 Selection of Timing of Dose for Each Subject

9.4.7 Blinding

An independent third-party vendor will develop the randomization schedule so that site personnel will not know treatment assignments. BMN 111 or placebo will be labeled with the study number and a unique identification number. Subjects and the participating site members will be blinded to the two study treatments (15 µg/kg BMN 111 or placebo). The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure. In the event of an emergency medical situation where subject management would be determined or significantly altered by knowing the treatment assignment, the investigator may be unblinded without prior written approval from the Medical Monitor. Following such an emergency unblinding, the investigator will contact the medical monitor and provide written rationale according to the unscheduled unblinding procedure set forth in the Study Manual. The Medical Monitor will review the rationale, evaluate whether there are any additional safety considerations that need to be implemented for the subject and/or the study, and determine whether the investigator requires further guidance on unblinding. The Medical Monitor may also communicate with the investigator advice on the care of the subject and define the plan for the subject's future participation in the study.

9.4.8 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 eCRF. The Investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

9.5 Treatment Compliance

Subjects will be instructed to return all used and unused BMN 111 or placebo kits at each study visit. Subject compliance with the dosing regimen will be assessed by reconciliation of

the used and unused vials. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided for the study.

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

9.6 Investigational Product Accountability (BMN 111 or Placebo)

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

9.6.1 Return and Disposition of Clinical Supplies

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

Unused BMN 111 or placebo may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for destruction. The study monitor must account for all BMN 111 or placebo kits/vials in a formal reconciliation process prior to destruction. The site must document all BMN 111 or placebo destroyed on site, and documentation must be provided to BioMarin and retained in the investigator study files. If a site is unable to destroy BMN 111 or placebo appropriately, the site can, upon request, return unused BMN 111 or placebo to the BioMarin contracted facility. The return of all BMN 111 or placebo kits/vials must also be documented and accounted for per instructions provided by BioMarin.

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

9.7 Dietary or Other Protocol Restrictions

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

Subjects should have adequate food intake prior to dosing. All subjects should have been well hydrated and fed in the hour prior to administration of BMN 111 or placebo.

9.8 Demographic Data and Medical History

Demographic data and a detailed medical history will be obtained at Screening. This 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; and evaluation for knee, thigh, hip or groin pain, or change in gait/activity.

9.9 Biological Parental Standing Height

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

9.10 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. Other body systems may be examined. Screening results will be the baseline values and clinically significant changes from baseline will be recorded as an AE or SAE and study drug related or unrelated when appropriate based on the investigator's clinical judgment.

9.11 Echocardiogram

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

9.12 Efficacy and Safety Variables

9.12.1 Efficacy and Safety Measurements Assessed

The Schedule of Events (Table 9.1.1 and Table 9.1.2) describes the timing of required evaluations.

9.12.2 Primary Efficacy Variables

The primary efficacy endpoint is change from baseline in length/height Z-score.

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

9.12.3 Secondary Efficacy Variables

The secondary efficacy endpoints include change from baseline in AGV (annualized to cm/yr), biomarker samples to evaluate the effect of BMN 111 on bone metabolism, BMN 111 pharmacodynamic biomarkers, growth parameters and body proportions, sleep apnea, skull and brain morphology, and clinical outcome assessments (developmental/functional/HRQoL status).

Weight will be measured at Screening and at study visits as indicated on the Schedule of Events (Table 9.1.1 and Table 9.1.2).

Biomarkers may include but are not limited to assessment of changes in bone and collagen metabolism (serum bone-specific alkaline phosphatase, serum collagen type X, and urine C-terminal telopeptide of collagen type II [CTX-II]) and BMN 111 bioactivity (plasma and urine cGMP). BioMarin or designee will perform analysis, and samples may also be used for assay development.

Samples for blood and/or urine biomarkers will be collected at the time points presented in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Refer to the Study Laboratory Manual for instructions regarding obtaining and shipping samples. The sample type will also be included in the Study Laboratory Manual.

9.12.3.1 Body Proportion Ratios of the Extremities

Change from baseline in body proportion ratios of the extremities will be evaluated using anthropometric measurements and measurement ratios. Refer to the Anthropometric Measurement Guidelines for specific instructions regarding the collection of growth measurements. All age-appropriate physical measurements will be collected at approximately the same time each visit (±2 hours around the time when the first measurement assessment was taken at Screening) by a trained study staff member; every effort will be made to have the measurements collected by the same study staff member, if possible, throughout the study. Each measurement will be taken in triplicate (excluding weight, taken once).

Anthropometric measurement can be conducted either pre-dose or post-dose. Measurements may include but are not limited to length, standing height (if able to stand unsupported), crown-to-rump length, head circumference, upper and lower arm and leg, and arm span. Measurements not taken in the midsagittal plane should be taken on the right side of the body if possible and should always be taken on the same side of the body throughout the study

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

9.12.3.2 MRI Assessments

MRIs are performed to evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular, and brain parenchymal dimensions. MRI assessment procedures for all visits must be performed as described in the Imaging Manual and can be conducted either pre-dose or post-dose.

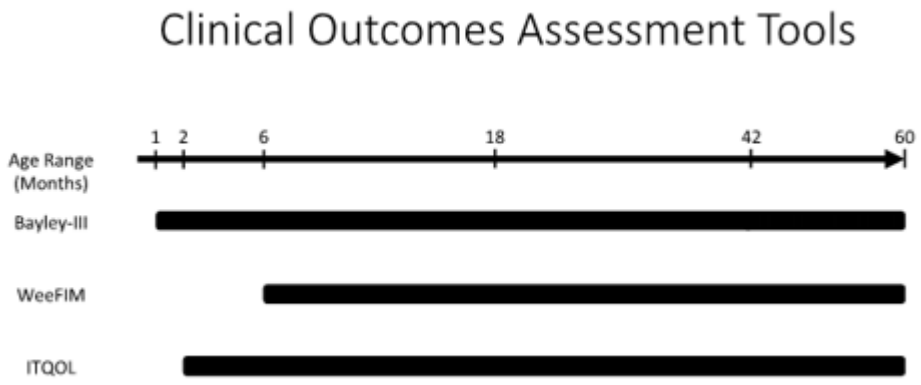
9.12.3.3 Sleep Study

Given that sleep apnea is a finding in children with ACH (Waters, 1993) and has implications on functional and health outcomes, a sleep study will be performed in a limited number of qualified sleep centers. A sleep-testing device will be used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea will include, but may not be limited to, the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index).

9.12.3.4 Clinical Outcome Assessments

Clinical outcome assessments will be administered to assess the HRQoL of study subjects. Functional Independence will be assessed. Clinical outcome assessments will be performed at the time points indicated in the Schedules of Events (Table 9.1.1 and Table 9.1.2) and the ITQoL should be administered prior to any other assessments. The Wee-FIM and the Bayley-III may be administered at any point deemed convenient during the visit. The age ranges for clinical outcome assessment tools are shown in Figure 9.12.3.4.1. The clinical outcome assessments are not to be considered as source data for AEs.

Figure 9.12.3.4.1: Clinical Outcomes Assessment Tools



9.12.3.4.1 Bayley-III

The Bayley-III is a performance-based outcome assessment for use in children from 1 to 42 months. It is individually administered by the trained clinician to the subject/child. The time required varies from 15-60 minutes depending on the child's developmental level and cooperation.

Scales include Cognitive subscale, Receptive and Expressive subscales, and Gross and Fine Motor subscales. The two language scales make up a composite Language Scale score and the Gross and Fine Motor subscales yield a composite Motor Scale score.

The scales have clinical and research utility as a diagnostic assessment for young children with varied disorders and disabilities, and reflect current professional standards for early childhood assessment (Bayley, 2006).

In addition to its use for subjects ranging from 1 to 42 months old, the Bayley-III assessment will be administered to those entering the study between 42 and 60 months old (Figure 9.12.3.4.1) and for the remainder of the duration of this study, as this assessment can capture ongoing developmental issues associated with Achondroplasia. Bayley-III is waived for subjects < 1 month old.

9.12.3.4.2 Functional Independence Measure (Wee-FIM)

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

The Wee-FIM instrument has been used in previous research in children with ACH, and has identified ongoing limitations in functional performance across these domains extending

beyond the age of 7 years (Ireland, 2011). Because the Wee-FIM considers the child's performance from a caregiver's perspective (Ireland, 2012), this tool in turn gives an indication of "burden of care" for families and caregivers of children with ACH. Wee-FIM is waived for children < 6 months old.

9.12.3.4.3 Infant and Toddler Quality of Life Questionnaire (ITQOL)

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

9.12.4 Exploratory Efficacy Variables

9.12.4.1 Clinical Photography

To document the physical and phenotypic findings of achondroplasia with and without treatment with study drug, clinical photography of the full body, face, spine, and extremities will be conducted. This assessment is optional. If the parents/caregivers decline clinical photography, the assessment will be waived for the duration of the study.

9.12.4.2 Exploratory Biomarker Research Sample Analyses

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

For each portion of the blood and urine samples reserved for protocol-specified analyses, there may be multiple sample aliquots. Once samples have been successfully analyzed during the study, unused sample portions may be used during the study for assay development or other purposes stated in this section. No exploratory genomic research will be conducted without consent from the subject and his/her legally authorized representative (parent or legal guardian).

9.12.4.3 Genomic Biomarker Analysis

While the inherited FGFR3 mutations associated with achondroplasia are well characterized, disease phenotype in monogeneic diseases is often modified by variants in other genes. Exploratory genomics will include, but are not limited to NPR-B, BRAF, and other genes associated with CNP signaling. Exploratory genomic analysis may inform understanding of

the BMN 111 mechanism of action in achondroplasia. This analysis will not be conducted without express consent from the subject and his/her legally authorized representative (parent or legal guardian).

9.12.5 Pharmacokinetics Variables

PK plasma samples will be collected pre-dose and at 5 (± 2 min), 15 (± 2 min), 30 (± 5 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post-dose. On Day 1, additional PK samples will be collected at 180 (± 5 min) and 240 (± 5 min) minutes. In the event of interruption of study drug administration for a sentinel patient on Day 1 when PK samples are scheduled, the collection of PK samples should be delayed until the subsequent day and only performed after successful administration of study drug has been completed in a single injection.

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

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

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

9.12.6 Safety Variables

Safety will be evaluated by the incidence of AEs, SAEs, and clinically significant changes in vital signs, physical examination, ECG, imaging, and laboratory test results (urinalysis, chemistry, hematology). Additionally, imaging, hip monitoring, biomarker, immunogenicity, cortisol and prolactin levels, and physical measurement data will be utilized for safety-related reviews and analysis.

9.12.6.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject receives study drug. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10.2.1. Assessments of AEs will occur at the time points shown in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Additionally, contact by a study staff member to the caregiver will be required every week for 6 months, and then every 2 weeks for the remainder of the study. During these contacts, study staff will ask the caregiver about dose administration and seek information on AEs and SAEs by specific questioning. Information on all AEs and SAEs should be recorded in the subject's medical record and on the AE eCRF.

9.12.6.2 Procedures During the Study

All concomitant procedures/interventions/surgeries will be recorded after informed consent is obtained and after the first administration of study drug, until end of study.

9.12.6.3 Imaging Assessment Procedures (per Schedule of Events)

Imaging assessment procedures for all visits must be performed using the same instruments. Imaging assessments can be conducted either pre-dose or post-dose.

- Bilateral X-rays of entire lower extremity, anterior-posterior (AP) view, to assess long bone growth and pathology as well as growth plate morphology.
- Lumbar spine X-rays to measure changes from baseline in bone morphology and pathology.
- DXA of whole body [less head], spine, to assess bone mineral density (BMD) and bone mineral content (BMC).

Additional imaging may be conducted should there be any issues or concerns with the subject's imaging assessments. Imaging assessments will be collected and interpreted by a central reader. If clinically significant abnormalities are noted, the investigator or designee is required to assess whether it is appropriate to report an AE and if the subject should continue in the study. Refer to the vendor Imaging Guidelines for detailed imaging assessment requirements and procedures.

9.12.6.4 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1 and Table 9.1.2. The scheduled clinical laboratory tests are listed in Table 9.12.6.4.1. Refer to the Study Reference 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.

The investigator should assess all abnormal clinical results and include a comment on whether or not the result is clinically significant. Each clinically significant laboratory result should be recorded as an adverse event.

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 eCRF.

Table 9.12.6.4.1: 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
Glucose		
Bicarbonate		Urine Chemistry Urine creatinine Urine sodium Urine potassium
LDH Phosphorus		
Total protein 25-hydroxy Vitamin D		
Creatinine Thyroid function (TSH, FT4; if either TSH and FT4 are abnormal then T3 may be measured in addition)		

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

9.12.6.5 Other Laboratory Assessments

Subjects will be asked to provide blood and urine at the times indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Blood volume for testing has been reduced to the minimum necessary for adequate evaluation of efficacy and safety of BMN 111.

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

Salivary cortisol and serum prolactin will be collected at the times indicated in the Schedule of Events (Table 9.1.1).

Scheduled biomarker and anti-BMN 111 antibody tests are listed in Table 9.12.6.5.1.

Table 9.12.6.5.1: Biomarkers and Anti-BMN 111 Antibodies

Blood Special Chemistry	Urine Biomarkers
Exploratory bone metabolism biomarkers: bone-specific alkaline phosphatase and collagen type X	Exploratory bone metabolism urine biomarkers: C-terminal telopeptide of collagen type II
Genomic biomarkers	BMN 111 pharmacodynamics biomarkers (cGMP)
Anti-BMN 111 antibodies	
BMN 111 pharmacodynamics biomarker (cGMP)	BMN 111 pharmacodynamics biomarker (cGMP)

cGMP, cyclic guanosine monophosphate

9.12.6.6 Child Behavior Checklist

The Child Behavior Checklist (CBCL) is for use in children from 1.5-5 years old, and will be administered for those entering the study at less than 5 years old and for the remainder of the duration of the study. The CBCL comprises 99 questions addressing symptoms related to mood, behavior issues, and sleep disturbance. It is completed by the parent or primary caregiver.

The form requires approximately 15 minutes to complete. The checklist yields scores in the following areas: reactivity, anxiety, depression, somatic complaints, withdrawal, sleep problems, attention problems, and aggressive behavior. CBCL is waived for children < 18 months old. The CBCL should be administered prior to any other study assessments.

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

Vital signs assessed pre-dose will include seated or supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). All treatment visits have pre-dose vital sign assessments. Post-dose measurements include heart rate and BP. For all dosing visits, assessment frequency is detailed in Table 9.12.6.5.1 (and Schedule of Events Table 9.1.1 and Table 9.1.2).

At Screening, after at least 5 minutes of rest, subject's BP is taken in sitting or supine position. Vital sign measurements should be repeated and documented 3 times, with at least 5-minute intervals between assessments. Left brachial arm should be the first method of assessment considered, and the same site should be used for blood pressure measurement in each subject throughout the study. The method and site of blood pressure measurement will be recorded and should be utilized consistently throughout the remainder of the study.

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

If a subject has signs 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 signs (if present) resolve. If the hypotension resolves within the first hour and returns to the normal range, additional BP monitoring as described above is not required. Detailed guidance for blood pressure measurements is provided in the Blood Pressure Instrument and Technique Guidelines.

Table 9.12.6.5.1: Vital Sign Assessment Frequency

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

1. Vital sign measurements are taken once per time point, preferably in a sitting or supine position, after at least 5 minutes of rest.
2. Heart rate, blood pressure, and respiratory rate should be taken and recorded at each indicated time point.
3. When blood samples and vital sign assessments are scheduled at the same time or within the same time window, vital signs should be measured before blood samples are drawn.
4. If a vital sign measurement must be taken after a blood draw, ensure adequate analgesia for the blood draw and wait several minutes before measuring vital signs.
5. Vital signs may be monitored more frequently or for longer duration post-dose as clinically indicated.
6. If a subject has a hypotensive event, or signs potentially consistent with hypotension, or a decrease of 20 mm Hg systolic BP or more from baseline (defined by pre-dose vitals collected that day), vital signs should be measured and recorded approximately every 15 minutes (± 5 minutes) for the first hour and every 30 minutes (± 5 minutes) thereafter until the BP returns to baseline (or within the normal range for this subject as defined by PI) and signs (if present) resolve.
7. If the decision is made to adjust the dose, vital signs will be obtained for at least 4 hr following the first dose at the adjusted dose level, similar to the Day 3, 8 schedule.
8. If a dose adjustment visit coincides with a visit at which a full PK is drawn, vital signs will be obtained for 8 hours, similar to the Day 1, 2 schedule.

9.12.6.8 Mitigating the Risk of Potential Hypotension

Study personnel and caregivers should be made aware of the potential risk of hypotension with BMN 111 administration. Subjects must be well hydrated and at a minimum be fed prior to administration of BMN 111 or placebo. If a recent acute illness associated with volume depletion (e.g., nausea, vomiting, diarrhea) has not completely resolved prior to the first dose of BMN 111 or placebo, BMN 111 or placebo dosing may be delayed until hydration status has improved (up to the maximum period allowed for the screening window).

Caregivers should be trained to observe and recognize the signs of dehydration (e.g. from fever, vomiting, diarrhea, etc.) and contact the investigator prior to BMN 111 or placebo

administration if dehydration is suspected. Site personnel and caregivers should be trained to identify the signs 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 10.3.1.4.

9.12.6.9 Electrocardiography

A standard 12-lead ECG will include heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. The time of collection will be recorded. ECGs should be performed in triplicate with the subject supine at the visits indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). ECGs will be performed post-dose on study day visits at which a dose is given; in addition, on Day 1, ECGs will be performed pre-dose. On days when PK samples are being drawn, ECGs should be performed within a 5-minute window prior to 30-minute PK assessment. 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.

9.12.6.10 Hip Clinical Assessment

The hip clinical assessment should be completed by an appropriately qualified physical therapist or a physician (MD) i.e., the investigator or the sub-investigator at the time points indicated in the Schedule of Events (Table 9.1.1 and Table 9.1.2). Medical history will be obtained to evaluate for hip, thigh, or knee pain, or change in gait. The physical exam (including observation of gait when possible) identifies and evaluates any changes in hip function or pain with assessment of active and passive range of motion. Changes from baseline may trigger further evaluation based on the investigator's clinical assessment, which may include hip imaging and/or orthopedic consultation. If findings on clinical hip exam are determined to be clinically significant by the investigator and in consultation with Sponsor's Medical Monitor and orthopedic specialist (if needed), the DMC will be notified of AEs resulting from clinically significant abnormal hip monitoring assessments. DMC may provide recommendations as to if/when BMN 111 or placebo treatment should be temporarily or permanently discontinued.

9.12.6.11 Pediatric Blood Volume

Clinical labs and immunogenicity samples are necessary to perform to adequate safety assessment in this study. The objectives of testing pharmacodynamics biomarkers are to demonstrate biologic activity of BMN 111 and to understand the impact of immune

responses on drug activity; and for blood biomarkers, to investigate the effects of treatment on changes in bone metabolism and endogenous CNP production.

To minimize blood collection volumes, assay technologies were chosen that are capable of sensitively detecting analytes using the lowest possible volume of blood for analysis. Additionally, assays capable of detecting analytes in urine rather than blood have been selected where possible.

9.12.6.12 Anti-BMN 111 Immunogenicity Assessments

Subjects randomized to receive BMN 111 or placebo will undergo immunogenicity testing. Blood (serum) samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 9.1.1), and testing performed using validated assays. Neutralizing antibody (NAb) testing will be performed on Baseline and TAb positive samples drawn from subjects weighing ≥ 7.0 kg and waived for subjects < 7.0 kg.

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

- Anti- BMN 111 total antibody (TAb)
- Anti-BMN 111 antibody cross-reactive with endogenous CNP, ANP, and BNP (TAb)
- Anti-BMN 111 NAb

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

9.12.6.13 HPA Axis Assessments

To address potential effects of BMN 111 on activation of the hypothalamic pituitary adrenal (HPA) axis, assessment of salivary cortisol and serum Prolactin levels will be analyzed at the time points indicated in the Schedule of Events (Table 9.1.1). Both tests will be done at Baseline, Week 26, and Week 52.

9.12.6.14 IgE Safety Assessments

Samples for total immunoglobulin E (IgE) and drug-specific IgE testing will be drawn on Day 1 and in the event of a significant hypersensitivity AE, or at the discretion of the investigator and/or BioMarin. A significant hypersensitivity AE is defined as an event that is grade 3 or higher, requires temporary or permanent cessation of BMN 111, or is determined to be significant at the discretion of investigator and/or BioMarin (excluding reactions that are solely a localized injection site reaction). If a hypersensitivity AE occurs, an unscheduled

safety visit should occur no later than 48 hours of the start of the reaction, including inspection of the injection site and clinical laboratory tests.

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

- Drug-specific IgE
- Total IgE
- Serum tryptase

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

A localized injection site reaction is defined as skin signs or signs 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).

9.12.6.15 Unscheduled Safety Visits

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

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

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

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

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 1 or more of the following criteria:

- Is fatal
- Is life threatening

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

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

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

10.1.3 Events of Special Interest (EOSI)

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

- Fracture
- Slipped Capital Femoral Epiphysis (SCFE)
- Avascular necrosis or Osteonecrosis

10.2 Methods and Timing for Capturing and Assessing Safety Parameters

10.2.1 Adverse Event Reporting Period

For subjects enrolled in Cohort 1 (≥ 24 to <60 months old) and Cohort 2 (≥6 to <24 months old), the study AE reporting period is as follows: after informed consent but prior to initiation of study treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, all non-serious AEs and SAEs reporting period begins and continues until 4 weeks following either the last administration of study drug or the early termination visit, whichever is longer (refer to Section 12.1.11). The criteria for determining, and the reporting of, SAEs is provided in Section 10.1.2. For subjects enrolled in Cohort 3 (0 to< 6 months old), the collection period for all AEs begins after informed consent is obtained.

10.2.2 Eliciting Adverse Events

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

10.2.3 Assessment of Seriousness, Severity, and Causality

The Investigator or qualified designee responsible for the care of the subject 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 (e.g., MD/DO, physician's assistant, nurse practitioner, or DDS).

10.2.3.1 Seriousness

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

10.2.3.2 Severity

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

The Investigator or qualified designee will determine the severity of each AE and SAE, and EOSI 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 activities of daily living (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 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 eCRF. 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 not be explained by factors or causes other than exposure to the IP **OR**
	• The administration of IP and the occurrence of the AE are reasonably related in time AND • The AE is more likely explained by exposure to the IP than by other factors or causes.

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

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

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

10.3 Procedures for Recording Adverse Events

10.3.1 Recording Adverse Events on a 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 (e.g., 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 sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, then this diagnosis should be entered on the AE form, replacing the original entries where appropriate.

10.3.1.2 Adverse Events Occurring Secondary to Other Events

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

10.3.1.3 Persistent or Recurrent Adverse Events

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

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

10.3.1.4 Hypotension

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

10.3.1.5 Injection Site Reactions

If an injection site reaction is associated with a single sign or symptom, report the event on AE eCRF page (e.g., redness at injection site, AE is injection site redness). If the injection site reaction is associated with multiple signs or symptoms, report injection site reaction as the adverse event on the AE page, and individual signs and symptoms will be reported on the ISR eCRF page (e.g., if the subject experiences redness and induration, report "Injection site reaction" on the AE page, and in the corresponding Injection eCRF page, report erythema and induration). If the injection site reaction appears after 24 hours, add "delayed" to the term used to describe the event.

10.3.1.6 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 it is not otherwise refuted by a repeat test to confirm the abnormality and **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 abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., 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.

10.3.1.7 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., *more frequent* headaches).

10.3.1.8 General Physical Examination Findings

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

10.3.1.9 Hospitalization, Prolonged Hospitalization, or Surgery

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

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

- Perform a protocol-mandated efficacy measurement

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

10.3.1.10 Deaths

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

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

10.4 Reporting Requirements

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

10.4.1 Expedited Reporting Requirements

All SAEs and EOSI, if applicable 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 entering the information in the AE eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. Each SAE must also be reported on the appropriate eCRF. Investigators should not wait to collect information that fully documents the event before notifying BPV of an SAE. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit any information requested by BioMarin as soon as it becomes available.

If the electronic data capture (EDC) is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

The reporting period for SAEs begins after informed consent is obtained and continues until 4 weeks following either the last administration of study drug or study discontinuation/termination, 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 Subjects after Adverse Events

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

For some SAEs, the Sponsor may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (eg, hospital discharge summary, consultant report, 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 subject to report, to the Investigator and/or to BPV directly, any subsequent SAEs that the subject's personal physician(s) believes might be related to prior study treatment.

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

10.7 Urgent Safety Measures

The regulations governing clinical trials state that the sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the 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 subjects, the sponsor and the Investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/EC/REB is notified at the same time."

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

The reporting period for these events which may require the implementation of urgent safety measures is the period from the time of signing of the ICF through the completion of the last study visit or at the Early Termination Visit (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
Phone: PI
Fax: PI
E-mail: drugsafety@bmrn.com

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

Name: PI, MD
PI
BioMarin Pharmaceutical Inc.
Address: 105 Digital Drive
Novato, CA 94949L
Phone: PI
Fax: PI
E-mail: PI

11 APPROPRIATENESS OF MEASUREMENTS

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

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

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

Bone-related biomarkers and other biochemical markers of the pharmacological activity of BMN 111 in the blood or urine are secondary assessments. Genomic biomarkers are exploratory assessments.

12 STUDY PROCEDURES

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

12.1 Treatment Visit(s)

12.1.1 Screening/Baseline Day -30 to Day -1

- Medical history
- Parental height
- Diagnostic genetic testing to confirm achondroplasia (if needed)
- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Echocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Thyroid function tests
- Vitamin D, 25-hydroxy test
- Salivary cortisol
- Serum prolactin
- Genomic blood biomarkers (optional)
- Bone metabolism blood biomarkers
- MRI brain/skull
- Sleep study
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: Wee-FIM
- Clinical outcome assessment: ITQOL
- Safety assessment: CBCL
- DXA
- AP and lateral X-rays of spine

- AP X-rays of lower extremities
- Clinical photographs (optional)
- Concomitant medications

12.1.2 Day 1 and Week 13 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Plasma pharmacokinetics and cGMP assessments
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.3 Days 2 and 3

- Physical examination
- Weight
- Vital signs
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo administration

- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.4 Day 8 (±1d) and Week 20 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Bone metabolism blood biomarkers
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.5 Week 3 (±7d)

- Physical examination
- Weight
- Vital signs
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo administration
- BMN 111 or placebo accountability

- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.6 Week 6 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Bone metabolism blood biomarkers
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.7 Week 26 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Salivary cortisol
- Serum prolactin
- Plasma pharmacokinetics and cGMP assessments
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic biomarkers

- Urine chemistry
- Hip monitoring
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: Wee-FIM
- Clinical outcome assessment: ITQOL
- Safety assessment: CBCL
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.8 Week 39 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Plasma pharmacokinetics and cGMP assessments
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications

- Phone call or home health visit

12.1.9 Week 52 (±7d)

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Thyroid function tests
- Vitamin D, 25-hydroxy test
- Salivary cortisol
- Serum prolactin
- Plasma pharmacokinetics and cGMP assessments
- Anti-BMN 111 immunogenicity
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry
- Hip monitoring
- MRI brain/skull
- Sleep study
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: Wee-FIM
- Clinical outcome assessment: ITQOL
- Safety assessment: CBCL
- DXA
- AP and lateral X-rays of spine
- AP X-rays of lower extremities
- Clinical photographs (optional)
- Capture concomitant procedures/interventions/surgeries

- BMN 111 or placebo administration
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications
- Phone call or home health visit

12.1.10 Week 56 Safety Follow-up (+7d)

- Physical examination
- Vital signs
- Electrocardiogram
- Echocardiogram
- Capture concomitant procedures/interventions/surgeries
- Adverse events
- Concomitant medications

12.1.11 Early Termination Visit

- Physical examination
- Weight
- Vital signs
- Electrocardiogram
- Echocardiogram (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
- Anthropometric measurements
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Salivary cortisol
- Serum prolactin
- Anti-BMN 111 immunogenicity
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- BMN 111 pharmacodynamic urine biomarkers
- Urine chemistry

- Hip monitoring
- MRI brain/skull (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
- Sleep study (obtained at the early termination visit only if the previous assessment was done more than 3 months prior to early termination)
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: Wee-FIM
- Clinical outcome assessment: ITQOL
- Safety outcome assessment: CBCL
- DXA
- AP and lateral X-rays of spine (obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination)
- AP X-rays of lower extremities (obtained at the early termination visit only if the previous assessment was done more than 6 months prior to early termination)
- Clinical photographs (optional)
- Capture concomitant procedures/interventions/surgeries
- BMN 111 or placebo accountability
- Adverse events
- Concomitant medications

12.2 Observational Period for Cohort 3 (Infants between birth and <3 months old [0 days to <13 weeks])

12.2.1 Screening Visit

- Medical history, including growth history and ACH-related history
- Concomitant medications
- Physical examination
- Vital signs
- Vitamin D, 25-hydroxy
- Alkaline phosphatase
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers

- Adverse events

12.2.2 Day 1 (Month 0)

- Concomitant medications
- Vital signs
- Anthropometric measurements
- Genomic biomarkers (optional)
- Weight
- Body mass index (calculated)
- Clinical outcome assessment: Bayley-III
- Clinical outcome assessment: ITQOL
- Capture concomitant procedures/interventions/surgeries
- Adverse events

12.2.3 3 Months (± 10 days)

- Concomitant medications
- Vital signs
- Anthropometric measurements
- Vitamin D, 25-hydroxy
- Alkaline phosphatase
- Bone metabolism blood biomarkers
- Bone metabolism urine biomarkers
- Weight
- Body mass index (calculated)
- Capture concomitant procedures/interventions/surgeries
- Adverse events

13 DATA QUALITY ASSURANCE

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

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

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

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS v. 9.4.

14.1.1 Interim Analyses

An interim analysis will be carried out to support NDA/MAA filing. The study team, subjects, and investigators will have no access to the individual subject treatment allocation, and blinded pooled safety outputs will be provided for the randomized subjects.

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

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

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

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

14.2 Safety Analysis

The safety analysis will be performed on safety population as defined in Section 14.7.2 and will be considered descriptive.

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

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment (as assessed by investigator), and severity. All AEs, including SAEs and AEs that lead to permanent discontinuation from the study and from the study treatment, will be listed. Hypersensitivity reactions and

symptomatic hypotension are of interest, and the percentage of subjects who report these AEs will be presented. Hypersensitivity reactions will be defined in the SAP.

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

All other safety measures including laboratory tests, vital signs, ECG, echocardiogram, hip clinical assessment, and concomitant medication data will also be summarized descriptively. Data summaries will be presented by treatment group (when applicable) for each cohort and overall. All safety results will be listed.

14.3 Efficacy Analysis

Efficacy analysis will be performed on the efficacy population as defined in Section 14.7.1. Efficacy endpoints include length/height AGV and length/height standard score (Z-score) at Week 52.

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

$$\text{AGV} = \frac{\text{Length/standing height at Day 2} - \text{Length/standing height at Day 1}}{\text{Interval Length (Days)}} \times 365.25$$

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

- Baseline: [Date of last length/height measurement in study 901 at least 6 months prior to Day 1 in study 206, Date of Day 1]
- Week 13: [Date of Day 1, Date of Week 13]
- Week 26: [Date of Day 1, Date of Week 26]
- Week 39: [Date of Day 1, Date of Week 39]
- Week 52 (12-month): [Date of Day 1, Date of Week 52]

The baseline of the AGV is established in the natural history study of Study111-901, based on the standing height measurements in the last 6 months prior to enrollment to Study 111-206. AGV will be summarized using descriptive statistics (mean, SD, median, minimum, and maximum). Results will be summarized by treatment group and cohort.

The measurement of length/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.

Comparisons between treatment groups by cohort on these variables will be carried out where appropriate. Statistical comparisons will be considered descriptive. Additional details regarding efficacy analysis will be provided in the SAP.

14.4 Pharmacokinetic Analyses

Subjects randomized to receive BMN 111 or placebo will undergo pharmacokinetic testing.

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

14.5 Immunogenicity Analysis

Immunogenicity will be summarized as change from baseline as well as by study time point in subjects randomized to receive BMN 111 or placebo. Results will be summarized as incidence and titer for all cohorts. Additionally, immunogenicity may be assessed for correlations with measures of safety, PK, and efficacy.

14.6 Determination of Sample Size

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

14.7 Analysis Populations

14.7.1 Efficacy Population

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

14.7.2 Safety Population

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

15 DATA MONITORING COMMITTEE

In addition to safety and PK 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. After the sentinel subjects complete 12 weeks of dosing, a DMC review will occur to evaluate all available safety and PK data. Upon approval by the DMC, the next younger cohort will be opened and the 3 sentinel subjects will be enrolled.

The DMC will make recommendations for stopping or continuing the study on an individual subject level and/or on a cohort level per the pre-specified stopping criteria. Based on criteria outlined in the protocol, the DMC may also make endorsements for dose adjustments if needed.

Please see DMC Charter for further details.

16 COSTS, COMPENSATION, AND SUBJECT INJURY

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

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

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

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

eCRFs must be completed using a validated web-based application. Study site personnel will be trained on the application and will enter the clinical data from source documentation, except in instances when electronic subject-reported data is transmitted directly into EDC, as referenced in the study specific vendor management plan. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representative) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If direct source document verification of study data by the site monitor is prohibited by institutional policy or local law, then the Investigator must make available facilities and/or personnel to allow GCP-compliant source verification to occur. Examples of such methods include certified copies of records which have study data visible but sensitive information redacted, or other GCP-compliant means agreed between the Investigator and the Sponsor.

A CRA designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" (SDV). Electronic Subject-reported data transferred directly into EDC will not be SDV'd or queried. If an error is discovered at any time or a clarification is needed, the CRA, or designee, will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Before a subject's eCRF casebook can be locked, data fields must be source data verified and all queries closed. Refer to the 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 eCRFs 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 sent to each site for retention with other study documents.

18 STUDY MONITORING AND AUDITING

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

Members of BioMarin's GCP Compliance Department or designees may conduct an audit of a clinical site at any time before, during, or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an 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.

19 RETENTION OF RECORDS

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

20 USE OF INFORMATION AND PUBLICATION

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

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572 and/or principles of ICH E6 GCP, the Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes. He or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and/or ICH E6 Sections 2.9 and 4.8 are met, as well as IRB/IEC review and approval requirements in 21 CFR Part 56 and/or ICH E6 GCP Section 2.6.
- 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 and/or ICH E6 GCP Section 4.11.
- 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 are in accordance with 21 CFR 312.62 and/or ICH E6 Section 4.9, and will make those records available for inspection in accordance with 21 CFR 312.68 and/or ICH Section 4.9.7.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH Section 3.0 and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312 and/or ICH E6 R2.

23 SIGNATURE PAGE

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

Protocol Number: 111-206A2

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

Investigator Signature Date

Printed name:

Accepted for the Sponsor:

PI

PI

Date

Printed name: PI MD

24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the major revisions and administrative changes made to the protocol body (corresponding changes have been applied in the synopsis but are not shown here) in Amendment 2, and relates the changes to the appropriate rationale (see pages 2-4). Text that has been added or inserted is indicated by underlined font, and deleted text is indicated by ~~strikethrough~~ font.

Section No./Title	Revision	Rationale
List of Abbreviations and Definitions of Terms	~~ADL Activity of Daily Living~~ CMC cervicomedullary compression CPAP continuous positive airway pressure CTX-II C-terminal telopeptide of cross-linked collagen type II CV% coefficient of variation DXA dual X-ray absorptiometry EDC electronic data capture EOSI events of special interest ERK extracellular signal-regulated kinase EU~~EudraCT~~ European Union~~ Drug Regulating Authorities Clinical Trials~~ ~~HR heart rate~~ HRQoL~~HRQOL~~ health-related quality of life IXRS Interactive Voice/Web Response System ~~mg milligram~~ ~~mL milliliter~~ ~~PA posterior-anterior~~ TAF human transcription factor Wee-FIM ~~WeeFIM~~ Functional independence measure for children	13
Section 7.3.1/Study 111-901	To obtain accurate baseline measurements, at least 6 months of growth data are collected for Cohorts 1 and 2; and at least 3 months of data for Cohort 3.	13
Section 7.4/Study Rationale	~~Study 111-202 is an ongoing Phase 2, open-label, sequential cohort, dose escalation study that assesses daily SC administration of BMN 111 in pediatric subjects with ACH, in which the primary objective is to evaluate the safety and tolerability of BMN 111 administered for 6 months and up to 24 months and includes secondary objectives consisting of~~	13

Section No./Title	Revision	Rationale
	~~determination of change from baseline in AGV, growth parameters, body proportions, and evaluation of the dose-exposure and PK profiles of BMN 111 in children with ACH.~~ ~~Analysis of safety data from the 6 month initial phase of Study 111-202 showed that treatment with BMN 111 was generally well tolerated at all dose levels (refer to current Investigators Brochure for specific details).~~ ~~Analysis of efficacy data from Study 111-202 demonstrated that that subjects given BMN 111 at the dose of 15 µg/kg daily had an improvement in AGV, with approximately ~ 50% increase over baseline seen with treatment for 6 months which was sustained after continued treatment for 12 months.~~ ~~Subjects treated with 30 µg/kg daily also showed similar improvement in mean AGV after 6 months and their mean changes from baseline in AGV were similar to subjects treated with 15 µg/kg daily. Safety data for the 30 µg/kg daily dose was also similar to the 15 µg/kg daily dose. Given that no clinically significant difference could be identified between the 15 µg/kg and 30 µg/kg daily dose in the Phase 2, 6 month safety and efficacy data, the lower of the two doses has been chosen for this Phase 2 study.~~	
8.0/Overall Study Design and Plan	The secondary objectives of the study are to: • Evaluate the effect of BMN 111 on change from baseline in AGV throughout the 52 weeks of the study • Evaluate the effect of BMN 111 on bone morphology/quality by X-ray and dual X-ray absorptiometry (DXA) • Evaluate the PK of BMN 111 in children age 0 to < 60 months with ACH • Evaluate hip function • Evaluate for hip, thigh, or knee pain, or change in gait • Evaluate the effect of BMN 111 on health-related quality of life (HRQoL), developmental status, and/ functional independence using age-specific QoL and functional independence questionnaires/~~QOL status~~ (Bayley Scales of Infant and Toddler Development, Third edition [Bayley-III], Activity of Daily Living and Functional Independence Measure (Wee-FIM), Infant Toddler Quality of Life Questionnaire (ITQOL),~~WeeFIM~~ Child Behavior Checklist (~~[~~CBCL~~]~~), ~~ITQOL~~ • Evaluate immunogenicity of BMN 111 and assess impact on safety, PK, and efficacy measures • Evaluate the effect of BMN 111 on bone metabolism and BMN 111 pharmacodynamic biomarkers ~~The exploratory objectives of the study are to:~~	1

Section No./Title	Revision	Rationale
	• Evaluate the effect of BMN 111 on growth parameters and body proportions, including change from baseline in upper:lower body segment ratio • Evaluate the effect of BMN 111 on sleep apnea ~~• Document physical and phenotypic changes with clinical photography (optional)~~ • Evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions • Describe the incidence of surgical interventions, including cervical decompression, adenotonsillectomy, and tympanostomy The exploratory objectives of the study are to: • Document physical and phenotypic changes with clinical photography (optional) • Evaluate genomic biomarkers (optional)	
Section 8.0/Overall Study Design and Plan	The exploratory objectives of the study are to: • Document physical and phenotypic changes with clinical photography (optional) • Evaluate genomic biomarkers (optional)	13
Section 8.0/Overall Study Design and Plan	• Evaluate the effect of BMN 111 on change from baseline in AGV throughout the 52 weeks of the study	13
Section 9.1/Overall Study Plan	Sentinel subjects from each cohort will be enrolled, treated with BMN 111, and studied for short-term safety and PK data~~, after which subjects in all 3 cohorts will be~~. No two sentinel subjects will be dosed on the same day for any cohort. After the sentinel data are evaluated, additional recruited subjects will be randomized to receive BMN 111 or placebo SC daily (1:1 ratio) for ~~up to~~ 52 weeks. ~~No two sentinel subjects will be dosed on the same day for any cohort.~~	13
Section 9.1/Overall Study Plan	Cohort 3 subjects must have a minimum of 3 months of observation prior to commencement of treatment. These subjects will have the option to enroll in either 111-901 or 111-206~~, depending on age at enrollment:~~ ~~• Infants ≥ 3 months and < 6 months old (≥ 13 weeks and < 26 weeks) will enroll in 111-901 for a 6-month period of pretreatment growth assessment prior to enrollment in 111-206 for treatment in Cohort 2.~~	13

Section No./Title	Revision	Rationale
	• ~~Infants between birth and < 3 months old (0 weeks and < 13 weeks) will enroll into 111-206 with a 3-month observational period prior to treatment.~~	
Table 9.1.1 and Table 9.1.2/ Schedules of Events	The schedules of events have been updated to reflect changes made elsewhere in the protocol text and table footnotes.	4
Table 9.1.1/ footnotes	[j] Growth measures may be collected in triplicate 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 length, standing height (if able to stand unsupported), crown-to-rump length, head circumference, upper and lower arm and leg, and arm span. Measurements not taken in the midsagittal plane should be taken on the right side of the body if possible and should always be taken on the same side of the body throughout the study. Anthropometric measures will be taken at the early termination visit only if subject discontinues after Week 6 and if > 2 weeks have elapsed since the previous assessment. [k] Clinical labs (hematology, chemistry, and urinalysis) are all pre-dose draws/samples and can be drawn collected anytime during the visit if there is no drug administration. n For optional genomic biomarkers, if the sample is not collected on Day 1, it may be drawn at any time during the study. The sample will be used for exploratory genomics including, but not limited to, NPR-B, BRAF, and other genes associated with CNP signalling. Bone metabolism blood biomarkers will be waived at screening for subjects weighing < 7.0 kg to limit the blood volume on the smallest subjects at this visit. Serum samples for bone metabolism biomarkers will be collected pre-dose on the indicated visits. Bone metabolism blood biomarkers include bone-specific alkaline phosphatase and collagen type X. s WeeFim Wee-FIM is waived for children < 6 months old; CBCL is waived for children < 18 months old. ITQOL and CBCL should be performed before any other assessments during the study visit. t Efforts to obtain a satisfactory image can be discontinued after 3 unsuccessful attempts. DXA at early termination visit only if subject discontinues after 9 months to reduce unnecessary radiation exposure (unless additional scans are recommended by investigator, BioMarin, or DMC). [u] AP and lateral lumbar spine, and AP lower extremities are obtained at the early termination visit only if the previous assessment was done more than 9 months prior to early termination (unless additional study is recommended by Investigator, BioMarin, or DMC). AP lower extremities X-ray at the Week 52 visit is waived for subjects who cannot stand upright unsupported. Although X-rays are preferable for consistency across the study population, if there are IRBs or IECs unwilling to allow x-rays in Cohort 3 subjects, contact the MM to discuss alternate non-radiological ~~methods for assessment~~. Obtained at ETV only if subject discontinues after 9 months to reduce unnecessary radiation exposure (unless additional X-rays are recommended by investigator, BioMarin, or DMC).	**5**

Section No./Title	Revision	Rationale
Section 9.2/Discussion of Study Design, Including Choice of Control Group	Therefore, to have a potential therapeutic benefit for subjects with ACH, specifically for the foramen magnum and spine, treatment is expected to be required prior to epiphyseal growth plate closure.	13
Section 9.3.1/Inclusion Criteria; Synopsis	Cohort 1 and 2 subjects must have at least a 6-month period of pretreatment growth assessment in Study 111 901 immediately before screening ~~study entry~~, and have one documented measurement of height/body length a minimum of 6 months ~~(+/- 10 days)~~ prior to the screening visit for 111-206. Cohort 3 subjects must have a minimum of 3 months of observation prior to treatment. This observational period can be obtained either (1) via prior enrollment in Study 111-901 or (2) via enrollment in this Study 111 206 for a minimum of 3 months of non-treatment observation prior to commencement of treatment.	13
Section 9.3.3/Inclusion Criteria for Cohort 3 Observation Period 9.3.4/Exclusion Criteria for Cohort 3 Observation Period	**9.3.3 Inclusion Criteria for Cohort 3 Observation Period** Individuals eligible to participate in this study must meet all of the following criteria: 1. Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research related procedure. Also, willing and able to provide written assent (if applicable) after the nature of the study has been explained and prior to performance of any research-related procedure. 2. Birth to ≤ 3 months of age at study entry. 3. Have ACH, documented by genetic testing 4. Are willing and able to perform all study procedures as physically possible After completing the observation period, subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug. **9.3.4 Exclusion Criteria for Cohort 3 Observation Period** 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) . . . 13. Concurrent disease or condition that, in the view of the Investigator, would interfere with study participation	**7**

Section No./Title	Revision	Rationale
	After completing the observation period, subjects must fulfill the general eligibility criteria prior to receiving treatment with study drug.	
Section 9.3.6/Removal of Subjects from Treatment or Assessment	Investigators may discontinue administration of BMN 111 or placebo at any time. Subjects discontinued from the study by the investigator must return to the clinic for a termination visit. Reasons for which the investigator or BioMarin will withdraw a subject from study treatment include, but are not limited to, the following: . . . . . . Therefore, subjects who discontinue study treatment should be encouraged to continue to undergo as many of the protocol-specified procedures and assessments as possible for the remainder of the study, as long as such continued participation does not detrimentally affect the health, safety, or welfare of the subject, and consent remains in place. It is important that following treatment discontinuation the original visit schedule is strictly adhered to.	13
Section 9.4.2.1/Product Characteristics and Labeling; Synopsis	The clinical drug product will be supplied in sterile, single-dose, Type I glass vials with coated stopper and flip-off aluminum cap. BMN 111 drug product is supplied as a 0.8-mg or 2-mg lyophilized, preservative-free, white-to-yellow powder for reconstitution with ~~either a sterile diluent or~~ sterile water for injection (WFI). The reconstituted solution is colorless to yellow and contains 0.8 mg/mL to 2 mg/mL of BMN 111, as well as citric acid, sodium citrate, trehalose, mannitol, methionine, polysorbate 80, and sterile WFI ~~water for injection~~. The target pH of the reconstituted solution is 5.5. Sterile WFI ~~water for injection~~ will be commercially sourced ~~and sterile diluent solution containing all of the above excipients will be supplied for reconstitution~~. All reconstitution and dose preparation steps will be performed as indicated in the BMN 111 Injection Guide and Injection video.	8
Section 9.4.4/Directions for Administration	The caregiver will be provided with a paper or electronic study diary and will be asked to record daily dosing information, changes in health status, medications and injection sites used, date and time of the injection, and injection site reactions, if any.	13
Section 9.4.5/Method of Assigning Subjects to Treatment Groups	Subjects will be randomized using an interactive voice/response system in a 1:1 ratio, i.e., injection with placebo:15 µg/kg of BMN 111~~, using IXRS~~. An independent third party vendor will develop the randomization schedule so that BioMarin and site personnel are blinded to treatment assignments. NOTE: In Japan, subjects are randomized separately within each cohort.	13
Section 9.4.7/Blinding	An independent third-party vendor will develop the randomization schedule so that ~~BioMarin~~ and site personnel will not know treatment assignments. BMN 111 or placebo will be labeled with the study number and a unique identification	13

Section No./Title	Revision	Rationale
	number. Subjects and the participating site members will be blinded to the two study treatments (15 µg/kg BMN 111 or placebo).	
Section 9.8/Biological Parental Standing Height	Standing height of the subject's biological parents (optional) may be assessed ~~(optional)~~ via height measurement or stated height. Height measurement can be done at any point in the study.	13
Section 9.11.4.2/Imaging Assessment Procedures	• Bilateral X-rays of entire lower extremity ~~x-rays~~, anterior-posterior (AP) view, to assess growth plate morphology. • Hip imaging via pelvis X~~x~~-ray to identify hip pathology • Lumbar spine X~~x~~-rays to measure changes from baseline in bone morphology and pathology. • MRI to evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions. • DXA ~~(BMD and BMC)~~ of whole body [less head], spine, and forearm (including ultra-distal, mid-distal, and one- third radius regions of interest) to assess bone mineral density (BMD) and bone mineral content (BMC).	13
Section 9.12.3/Secondary Efficacy Variables	The secondary efficacy endpoints include change from baseline in AGV (annualized to cm/yr), biomarker samples to evaluate the effect of BMN 111 on bone metabolism, and BMN 111 pharmacodynamic biomarkers, growth parameters and body proportions, sleep apnea, skull and brain morphology, and clinical outcome assessments (developmental/functional/HRQoL status).	9
9.12.3.2/MRI Assessments	**9.11.4.2 ~~Imaging~~ MRI Assessments** ~~Imaging assessment procedures for all visits must be performed using the same instruments. Imaging assessments can be conducted either pre-dose or post-dose.~~ ~~• Bilateral lower extremity x-rays, anterior-posterior (AP) view, to assess growth plate morphology.~~ ~~• Hip imaging via pelvis x-ray to identify hip pathology~~ ~~• Lumbar spine x-rays to measure changes from baseline in bone morphology and pathology.~~ MRIs are performed to evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular, and brain parenchymal dimensions. MRI assessment procedures for all visits must be performed as described in the Imaging Manual and can be conducted either pre-dose or post-dose.	3
Section 9.12.3.4/Clinical	Clinical outcome assessments will be administered to assess the HRQoL ~~health-related quality of life~~ of study subjects. Functional Independence ~~ADL questionnaires~~ will be assessed. ~~performed in study subjects to assess functional performance.~~ Clinical outcome assessments will be performed at the time points indicated in the Schedules of Events	13

Section No./Title	Revision	Rationale
Outcome Assessments	(Table 9.1.1 and Table 9.1.2) and the ITQoL and CBCL should be administered prior to any other assessments. The Wee-FIM and the Bayley-III may be administered at any point deemed convenient during the visit.~~)~~. The age ranges for clinical outcome assessment tools are shown in Figure 9.12.3.3.1 The clinical outcome assessments are not to be considered as source data for AEs. Figure 9.12.3.3.1 has been modified to remove the CBCL as a Clinical outcome assessment tool.	
9.12.3.4.2	~~9.12.4.7.2~~ **9.12.3.4.2** ~~**Activity of Daily Living and**~~ **Functional Independence Measure (Wee-FIM)**	13
Section: 9.12.5/Pharmacokinetics Variables	Whenever possible, the following PK parameters for sentinel subjects and for subjects randomized to BMN 111 will be estimated by non-compartmental analysis: • Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) • Area under the plasma concentration-time curve from time 0 to the time of last measurable concentration (AUC_{0-t}) • Maximum observed plasma concentration (C_{max}) • Time to reach C_{max} (T_{max}) • ~~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)	10
9.12.6.2/Procedures During the Study	All concomitant procedures/~~intervention/surgery~~ interventions/surgeries will be recorded after informed consent is obtained and after the first administration of study drug, until end of study.	13
9.12.6.3/Imaging Assessment Procedures (per Schedule of Events)	~~9.11.4.2~~ **9.12.3.2 Imaging Assessment Procedures (per Schedule of Events)** Imaging assessment procedures for all visits must be performed using the same instruments. Imaging assessments can be conducted either pre-dose or post-dose. • Bilateral lower extremity x-rays, anterior-posterior (AP) view, to assess long bone growth and pathology as well as growth plate morphology. • ~~Hip imaging via pelvis x-ray to identify hip pathology~~ • Lumbar spine x-rays to measure changes from baseline in bone morphology and pathology.	2

Section No./Title	Revision	Rationale
	• ~~MRI to evaluate the effect of BMN 111 on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions.~~ • DXA ~~(BMD and BMC)~~ of whole body [less head]~~,~~ and spine~~, and forearm (including ultra-distal, mid-distal, and one third radius regions of interest)~~ to assess bone mineral density (BMD) and bone mineral content (BMC). ~~Although X-rays are preferable for consistency across the study population, if there are IRBs or IECs unwilling to allow X-rays in Cohort 3 subjects, contact the medical monitor to discuss alternate non-radiological methods for assessment.~~	
Section 9.12.6.6/Child Behavior Checklist	**~~4.12.3.3~~ 9.12.6.6 Child Behavior Checklist** The Child Behavior Checklist (CBCL) is for use in children from 1.5-5 years old, and will be administered for those entering the study at less than 5 years old and for the remainder of the duration of the study. The CBCL comprises 99 questions addressing symptoms related to mood, behavior issues, and sleep disturbance. It is completed by the parent or primary caregiver. The form requires approximately 15 minutes to complete. The checklist yields scores in the following areas: reactivity, anxiety, depression, somatic complaints, withdrawal, sleep problems, attention problems, and aggressive behavior. CBCL is waived for children < 18 months old. The CBCL should be administered prior to any other study assessments.	**6**
Section 9.12.6.10 Section 9.12.6.12	**Anti-BMN 111 Immunogenicity Assessments and ~~IgE Testing~~** **~~Ad Hoc~~ IgE Safety Assessment**	13
Section 10.8/BPV Contact Information	Name: PI PI MD~~, PhD~~ PI BioMarin Pharmaceutical Inc. Address: ~~10 Bloomsbury Way~~ ~~London WC1A 2SL105~~ Digital Drive Novato, CA 94949L Phone: PI	13

Section No./Title	Revision	Rationale
	PI Fax: PI PI E-mail: PI PI	
Section 12.1.1/Screening/ Baseline Day -30 to Day -1	• Serum prolactin • Genomic blood biomarkers (optional) • Bone metabolism blood biomarkers • ~~Screening baseline hip assessment with pelvis x ray~~ • MRI brain/skull • Sleep study • Clinical outcome assessment: Bayley-III • Clinical outcome assessment: ~~WeeFIM~~Wee-FIM • Clinical outcome assessment: ITQOL • ~~Clinical outcome~~Safety assessment: CBCL	13
12.1.2/Day 1/Week 13 (±7d)/12.1.2 Days 2 and 3/12.1.4 Day 8 (±1d)/Week 20 (±7d)/12.1.5 Week 3 (±7d;)	• Capture ~~all~~concomitant procedures/interventions/surgeries	13
12.1.6/Week 6 (±7d)	• ~~Genomic biomarkers (optional)~~	13

Section No./Title	Revision	Rationale
	• Bone metabolism blood biomarkers • Capture ~~all~~concomitant procedures/interventions/surgeries	
12.1.7/Week 26 (±7d)	• Clinical outcome assessment: ~~WeeFIM~~Wee-FIM • Clinical outcome assessment: ITQOL • ~~Clinical outcome~~Safety assessment: CBCL • Capture ~~all~~concomitant procedures/interventions/surgeries	13
12.1.8/Week 39 (±7d)	• Capture ~~all~~concomitant procedures/interventions/surgeries	13
12.1.9/Week 52 (±7d)	• Genomic biomarkers (optional) • Clinical outcome assessment: ~~WeeFIM~~Wee-FIM • Clinical outcome assessment: ITQOL • ~~Clinical outcome~~Safety assessment: CBCL • Capture ~~all~~concomitant procedures/interventions/surgeries	13
12.1.10/Week 56 Safety Follow-up (+ 7d)	• Capture ~~all~~concomitant procedures/interventions/surgeries	13
12.1.11/Early Termination Visit	• Clinical outcome assessment: ~~WeeFIM~~Wee-FIM • Clinical outcome assessment: ITQOL • ~~Clinical~~Safety outcome assessment: CBCL • Capture ~~all~~concomitant procedures/interventions/surgeries	13
12.2.2/Day 1 (Month 0)	• Capture ~~all~~concomitant procedures/interventions/surgeries	13

Section No./Title	Revision	Rationale
12.2.3/3 Months (± 10 days)	• Capture ~~all~~concomitant procedures/interventions/surgeries	13
Section 13 Data Quality Assurance	Sites will enter study data into eCRFs into the study EDC system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications. Additional subject-reported study data may be entered into the study EDC system via electronic diary.	11
Section 14.1.1/Interim Analysis	An interim analysis will be carried out to support NDA/MAA filing. The ~~report will be provided by a third party to assure that the~~ study team, subjects, and investigators will have no access to the individual subject treatment allocation, and blinded pooled safety outputs will be provided for the randomized subjects.	13
Section 14.3/Efficacy Analysis	AGV will be calculated for the following visits/intervals: Baseline: [Date of last length/height measurement in study 901 at least 6 months prior to ~~screening visit~~Day 1 in study 206, Date of Day 1]	13
Section 17 Case Report Forms and Study Documents	eCRFs must be completed using a validated web-based application. Study site personnel will be trained on the application and will enter the clinical data from source documentation, except in instances when electronic subject-reported data is transmitted directly into EDC, as referenced in the study specific vendor management plan. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable. A CRA designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" (SDV). Electronic Subject-reported data transferred directly into EDC will not be SDV'd or queried.	11