Official Title: A Phase 2, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Pediatric Patients < 18 years of age with CLN2 Disease

NCT Number: NCT02678689

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 05 February 2019

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Pediatric Patients < 18 years of age with CLN2 Disease
Protocol Number:	190-203
Investigational Product:	Cerliponase alfa (BMN 190), recombinant human tripeptidyl peptidase-1 (rhTPP1)
IND/EudraCT Number:	IND 122472 / EudraCT 2015-000891-85
Indication:	CLN2 disease due to tripeptidyl peptidase-1 (TPP1) deficiency
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Sponsor Medical Monitor:	PI MD PI , Rare Disease
Study Design:	Phase 2 open-label, multicenter study
Comparison:	Untreated historical controls (data from siblings affected by CLN2 disease and/or data from a CLN2 disease patient registry)
Duration:	Surgery/recovery of 14-28 days with treatment for at least 144 weeks
Dose:	BMN 190 administered by intracerebroventricular (ICV) infusion every 14 days as follows: • Birth to < 6 months: 100 mg • 6 months to < 1 year: 150 mg • 1 year to < 2 years: 200 mg (first 4 doses), 300 mg (subsequent doses) • ≥2 years: 300 mg
Date of Original Protocol:	23 October 2015
Date of US-Specific Protocol:	27 April 2016
Date of Amendment 1:	31 January 2017
Date of Amendment 2:	17 March 2017
Date of Amendment 3:	05 May 2017
Date of Amendment 4	20 October 2017
Date of Amendment 5	17 December 2018
Date of Amendment 6	05 February 2019

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 6

Date: 05 February 2019

SUMMARY OF CHANGES AND RATIONALE

1. The purpose of this amendment is to correct an error in Protocol 190-203 Amendment 5 in which "Ophthalmology Assessments" (Baseline/First Infusion, Q48W, Study Completion/Early Termination) was inadvertently removed from the Schedule of Events (Table 9.1.1) and Study Procedures (Section 12). Ophthalmologic assessments for the 190-203 protocol should continue to be performed before the first infusion and every 48 weeks for the duration of the study.

Refer to Section 25 for a summary of the amendment revisions.

2 SYNOPSIS

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 **NAME OF FINISHED PRODUCT:** Cerliponase alfa (BMN 190) **NAME OF ACTIVE INGREDIENT:** recombinant human tripeptidyl peptidase-1 (rhTPP1)	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**
TITLE OF STUDY: A Phase 2, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Pediatric Patients < 18 years of age with CLN2 Disease		
PROTOCOL NUMBER: 190-203		
STUDY SITES: Approximately 4 clinical sites worldwide		
PHASE OF DEVELOPMENT: Phase 2		
STUDY RATIONALE: BMN 190 is a recombinant form of human tripeptidyl peptidase-1(TPP1), the enzyme deficient in CLN2 disease (also known as classical late-infantile CLN2, cLINCL, or Jansky-Bielschowsky disease), which is a type of Batten Disease. As an enzyme replacement therapy (ERT), intracerebroventricular (ICV) BMN 190 is expected to restore TPP1 enzyme activity in the brain and alter neurological disease progression. Given the urgent and severe unmet medical need in CLN2 disease, results in nonclinical models of disease and the BMN 190-201 clinical study, this study is designed to ascertain the safety and efficacy of treatment before significant disease burden occurs. CLN2 disease is a pediatric neurodegenerative disorder characterized predominantly by late infantile onset with subsequent rapid, irreversible clinical decline. Murine and canine models of CLN2 disease have shown significant treatment benefit with CNS delivery of BMN 190. TPP1-null dachshunds dosed with BMN 190 early in life had delayed onset of clinical signs, preserved motor and cognitive function, and prolonged life. Response to ERT earlier in this and other animal models, indicates the importance of early treatment. BMN 190 has been tested in children with CLN2 disease ≥ 3 years of age. Results from the 190-201 study demonstrated a substantial improvement of the rate of clinical progression in children treated with BMN 190 compared with untreated historical controls. Further, in those children who had received at least 48 weeks of BMN 190 dosing, clinical scores stabilized, in contrast to matched historical untreated controls in which decline was rapid and profound in the majority of matches. Based on clinical and nonclinical information, it appears that early BMN 190 intervention has the potential of preventing or postponing clinical decline for a significant period. This protocol is intended to investigate the safety and tolerability of ICV-delivered BMN 190 in CLN2 patients.		

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 **NAME OF FINISHED PRODUCT:** Cerliponase alfa (BMN 190) **NAME OF ACTIVE INGREDIENT:** recombinant human tripeptidyl peptidase-1 (rhTPP1)	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

The efficacy of BMN 190 as a delay in disease progression will be evaluated relative to untreated historical controls (data from siblings affected by CLN2 disease and/or data from a CLN2 disease patient registry).

OBJECTIVES:

The primary objectives of this study include the following:

- evaluate safety and tolerability of BMN 190 administered via intracerebroventricular (ICV) device
- evaluate treatment effectiveness as a delay in progression of motor-language (ML) score on the Hamburg CLN2 clinical rating scale
- assess immunogenicity of BMN 190 in CSF and serum

Secondary objectives of this study include the following:

- characterize the PK of BMN 190 in CSF and plasma
- measure MRI parameters of disease progression
- assess impact of treatment on the total Hamburg clinical rating scale
- assess the time to disease manifestation for asymptomatic patients

Exploratory objectives of this study include the following:

- assess development achievement
- assess abnormal involuntary movements
- evaluate retinal anatomy using optical coherence tomography (OCT)
- determine seizure onset, type and frequency
- determine change in seizure activity
- anti-epileptic treatment
- assess quality of life
- assess changes in EEG
- assess changes in visual acuity
- analysis of disease-related biomarkers from CSF and blood

STUDY DESIGN AND PLAN:

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 **NAME OF FINISHED PRODUCT:** Cerliponase alfa (BMN 190) **NAME OF ACTIVE INGREDIENT:** recombinant human tripeptidyl peptidase-1 (rhTPP1)	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

BMN 190 is a recombinant human TPP1 used for the treatment of CLN2 disease, which is predominantly a late infantile presentation of neuronal ceroid lipofuscinosis, one of the genetic isoforms of Batten disease.

This is a Phase 2 open-label, multicenter study in pediatric patients < 18 years of age with CLN2 disease, confirmed by deficiency of TPP1 enzyme activity and mutation of the *CLN2* gene. The study is designed to assess disease progression in CLN2 patients treated with BMN 190 compared to natural history data from untreated historical controls (data from a CLN2 disease patient registry and data from siblings with CLN2 disease, when available). The comparison of treatment with untreated controls will be compared from the time of the initiation of study drug. Eligibility will be determined and study enrollment will occur before patients are admitted to the hospital for surgical implantation of an ICV access device. Baseline values will be recorded before the first infusion, which will occur at least 14 days from surgery and no more than 28 days after surgery. BMN 190 is then administered every 14 days (± 3 days) by ICV infusion according to the patient's age:

- birth to < 6 months: 100 mg
- 6 months to < 1 year: 150 mg
- 1 year to < 2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- ≥2 years: 300 mg

Patients younger than 2 years will start the study at the dose level appropriate for their age and will transition to the dose level consistent with their age as they mature.

The study will enroll at least 10 patients: at least 5 patients with a Hamburg CLN2 scale ML score ≥ 5 points, at least 5 patients with a ML score < 5 points, and at least 5 patients < 2 years of age. The treatment period is at least 144 weeks. Upon study completion or early termination, all patients will be given the opportunity to participate in a postmarketing registry that will assess the long-term safety and efficacy of BMN 190 for patients receiving commercial drug.

Patients in this study will be required to have an ICV reservoir surgically implanted for administration of BMN 190. An MRI will be performed in advance of the procedure to ensure proper planning and placement of the ICV access device. Patients will be monitored closely in a nursing-intensive environment for 48 hours post-ICV device placement and after the start of the first drug infusion. Following ICV access device placement, subjects and their caregivers will be given written instructions providing details on signs and symptoms of concern for device complications and instruction on when to return to the site for device evaluation. These instructions should be provided by the institution and be based on local standard of care. An additional follow-up phone call will be conducted within 48 hours of inpatient discharge for all visits.

Age-specific dosing will be initiated every 14 days (±3 days) from the date of first infusion. The normal infusion will be administered over 4 (±1) hours at a rate of 2.5 mL/hr; the dose will be determined by the patient's age. Subjects not receiving the full 300 mg dose (administered in a total volume of 10 mL) will receive the appropriate volume at a rate of 2.5 mL/hr for over a shorter duration of time.

Age	Dose	Rate	Infusion Time
birth to < 6 months	**100 mg**	**2.5 mL/hr**	**1.3 hours (±0.5 hr)**
6 months to < 1 year	**150 mg**	**2.5 mL/hr**	**2 hours (±0.5 hr)**
1 year to < 2 years	**200 mg (first 4 doses),** **300 mg (subsequent doses)**	**2.5 mL/hr** **2.5 mL/hr**	**2.7 hours (±1 hr)** **4 hours (±1 hr)**
≥2 years	**300 mg**	**2.5 mL/hr**	**4 hours (±1 hr)**

Dosing can be adapted in the judgement of the investigator (and in consultation with the medical monitor) to manage adverse events (AEs) as outlined in the table above. Should the dose-limiting AE resolve in the opinion of the investigator, the dosing at the full specified dose may resume.

In patients younger than 2 years, dosing may also be adjusted by the sponsor in consultation with the investigator and medical monitor based on results from PK analysis, as follows:

- Within a patient, if the observed CSF $AUC_{0\text{-}t}$ exceed the range of CSF $AUC_{0\text{-}t}$ characterized with the 300 mg dose in Study 190-201, the dose may be reduced to 50% of the recommended age-appropriate dose.
- Within a patient, if the observed CSF $AUC_{0\text{-}t}$ is less than the range of CSF $AUC_{0\text{-}t}$ characterized with the 300 mg dose in Study 190-201, the dose may be increased to the recommended dose for the next oldest age group.

For all infusions, subjects will be monitored in an appropriate inpatient setting for a minimum of 24 hours from the start of the infusion. For the first infusion only, subjects will also return for a

follow-up visit to clinic 72 hours (and no later than the third calendar day) after the start of infusion. After all visits, the parent or legal guardian will be telephoned within 48 hours to determine health status.

Efficacy will be measured using the 0 to 6-point ML score on the Hamburg CLN2 rating scale as the primary endpoint. The 12-point total score (motor, language, vision, and seizure subscales) on the Hamburg CLN2 scale, time to disease manifestation (for asymptomatic patients), and MRI measures of disease progression will be collected as secondary endpoints. Exploratory efficacy measures will include developmental status, involuntary movements, retinal anatomy using OCT, seizure frequency, change in seizure activity (as measured by Hamburg score), anti-epileptic treatment, quality of life metrics, changes in EEG, assessment of visual acuity, and analysis of disease-related biomarkers.

The safety and tolerability of treatment will be assessed by collection of AEs, physical findings, vital signs, ECGs, and clinical laboratory tests. AEs will be assessed by the investigator for severity, seriousness, and relationship to study drug and/or the ICV access device. An AE occurring within 24 hours of the start or restart of BMN 190 infusion will be defined as a temporally related event (TRE).

To date, there has been no anaphylaxis or anaphylactoid reactions in studies with BMN 190. However, in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or severe hypersensitivity (defined as a hypersensitivity event of Grade 3 or higher), blood samples to assess C4, serum tryptase, and total IgE will be collected within 1 hour of the event and tested; a blood sample to assess drug-specific IgE will be collected no sooner than 8 hours after the event (or before the next infusion).

In addition, the investigator must contact the BioMarin medical monitor within 1 business day if any AE is severe (Grade 3 or higher) or serious and requires any of the following:

- infusion interruption, discontinuation, or modification (not due to blocked line)
- administration of IV fluids, steroids, or antihistamines
- administration of oxygen

Before subsequent infusions, the study site investigator and BioMarin medical monitor will discuss the case and agree upon infusion modification or additional premedication, if necessary. Agreed upon dose modifications or introduction of additional premedication should be documented in the Case Report Forms and source files.

AEs will be judged by relationship to study drug and to the ICV access device. Routine CSF surveillance will be performed by clinical laboratories and microbial studies each time the reservoir is accessed. If an infection is suspected, blood and CSF samples will be drawn for laboratory assessments. The subsequent course of therapy may include antibiotic therapy and catheter reposition or withdrawal. If BMN 190 treatment is suspended, BMN 190 may resume if no more than 4 consecutive doses are missed after the last given dose.

Samples will also be taken to evaluate the BMN 190 immunogenicity in CSF and serum.

NUMBER OF SUBJECTS PLANNED:

At least 10 patients are expected to be enrolled: at least 5 patients with a Hamburg ML score $\geq$ 5 points, at least 5 patients with a ML score < 5 points, and at least 5 patients < 2 years of age.

DIAGNOSIS AND ENTRY CRITERIA:

Pediatric patients (from birth to < 18 years of age) with confirmed CLN2 disease are eligible to participate in this study. Additional criteria for participation in this study are detailed below. Subjects must satisfy the following entry criteria in order to enroll in the study.

Inclusion Criteria:

- Diagnosis of CLN2 disease as determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at Screening. *Note: Blood for TPP1 enzyme activity and CLN2 gene analysis must be collected to be analyzed centrally.*
- Quantitative clinical assessment of the Hamburg motor-language aggregate score 3-6 at Screening, as defined in the Ratings Assessment Guideline.
- < 18 years of age at the time of informed consent
- Written informed consent from parent or legal guardian and assent from subject, if appropriate
- Males and females who are of reproductive age should practice true abstinence, defined as no sexual activity, during the study and for 6 months after the study has been completed (or withdrawal from the study). If sexually active and not practicing true abstinence, males and females of reproductive age must use a highly effective method of contraception while participating in the study.
- Ability to comply with protocol required assessments (ICV implantation, drug administration, laboratory sample collection, EEG, ECG, MRI, etc.)

Exclusion Criteria:

- Another inherited neurologic disease, e.g., other forms of CLN or seizures unrelated to CLN2 disease (patients with febrile seizures may be eligible)
- Another neurological illness that may have caused cognitive decline (e.g., trauma, meningitis, hemorrhage) or interfere with disease rating (autism) before Screening
- Percutaneous feeding tube placement prior to enrollment
- Has received stem cell, gene therapy, or ERT
- Contraindications for neurosurgery (e.g., congenital heart disease, severe respiratory impairment, or clotting abnormalities)
- Contraindications for MRI scans (e.g., cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain)
- Episode of generalized motor status epilepticus within 4 weeks before the First Dose visit
- Severe infection (e.g., pneumonia, pyelonephritis, or meningitis) within 4 weeks before the First Dose visit (enrollment may be postponed)
- Presence of ventricular abnormality (hydrocephalus, malformation)
- Presence of ventricular shunt
- Has known hypersensitivity to any of the components of BMN 190

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- Has received any investigational medication within 30 days before the first infusion of study drug or is scheduled to receive any investigational drug other than BMN 190 during the course of the study
- Has a medical condition or extenuating circumstance that, in the opinion of the investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability
- Pregnancy any time during the study; a female subject judged by the investigator to be of childbearing potential will be tested for pregnancy

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INVESTIGATIONAL PRODUCT, DOSE, ROUTE AND REGIMEN:

BMN 190 will be administered by ICV infusion every 14 days (preferably in the morning) according to the patient's age:

- birth to < 6 months: 100 mg
- 6 months to < 1 year: 150 mg
- 1 year to < 2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- ≥2 years: 300 mg

Patients younger than 2 years will start the study at the dose level appropriate for their age and will transition to the dose level consistent with their age as they mature.

Fasting for a minimum of 2 hours may be considered for the first infusion and subsequent infusions until the subject's reaction to the study drug is determined. When a feeding tube is used, the tube may be turned off 2 hours before infusion.

The normal infusion will be administered over 4 (± 1) hours at a rate of 2.5 mL/hr; the dose will be determined by the patient's age. Subjects not receiving the full 300 mg dose (administered in a total volume of 10 mL) will receive the appropriate volume at a rate of 2.5 mL/hr for over a shorter duration of time.

Dosing can be adapted in the judgement of the investigator (and in consultation with the medical monitor) to manage adverse events (AEs) as outlined in the table above. Should the dose-limiting AE resolve in the opinion of the investigator, the dosing at the full specified dose may resume.

In patients younger than 2 years, dosing may also be adjusted by the sponsor in consultation with the investigator and medical monitor based on results from PK analysis, as follows:

- Within a patient, if the observed CSF AUC_{0-t} exceed the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be reduced to 50% of the recommended age-appropriate dose.
- Within a patient, if the observed CSF AUC_{0-t} is less than the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be increased to the recommended dose for the next oldest age group.

REFERENCE THERAPY, DOSE, ROUTE AND REGIMEN:

Because practical and ethical concerns preclude contemporaneous or untreated control subjects, comparison will be with historical data from existing CLN2 disease registries and data from siblings with CLN2 disease, when available.

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DURATION OF TREATMENT:

Treatment will continue for at least 144 weeks or until all procedures are completed or the subject discontinues from the study.

CRITERIA FOR EVALUATION:

Safety:

- AEs and concomitant medication
- routine clinical laboratory tests (hematology, chemistry, and urinalysis)
- routine CSF surveillance (cell count, protein, glucose, and culture)
- vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, respiration rate, and temperature)
- physical examination
- neurological examination
- electrocardiogram (ECG), 3 or 5-lead, 12-lead
- immunogenicity, includes anti-BMN 190 total antibodies (TAb) and neutralizing antibodies (NAb) in CSF; TAb, NAb, total IgE, and drug-specific IgE in serum

Efficacy:

- Hamburg CLN2 disease rating scale with videotaping: 0 to 12 point total score (motor, language, visions, and seizure subscales)
    - Change in seizure activity (clinical [0 to 3 point Hamburg CLN2 rating scale, seizure subscale])
- Anti-epileptic treatment
- Denver Development Scale II
- Modified Unified Batten Disease Rating Scale Involuntary Movement Scale (mUBDRS-Movement)
- Modified Unified Batten Disease Rating Scale Seizure Inventory (mUBDRS-Seizure)
- Time to disease manifestation for asymptomatic patients (time to first seizure)
- Assessments of visual acuity

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Imaging:

- Cranial MRI with measurements of atrophy and apparent diffusion coefficients
- Optical coherence tomography (OCT)
- Electroencephalogram (EEG)

Quality of Life Tests:

- PedsQL: Family Impact and infant/toddler modules
- CLN2- specific QOL

Pharmacokinetics:

- area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
- area under the concentration-time curve from 0 to time of last measurable concentration (AUC_{0-t})
- maximum concentration (C_{max})
- time to reach C_{max} (T_{max})
- elimination half-life (t1/2)
- apparent clearance of drug (CL/F)
- apparent volume of distribution based on terminal phase (V_z/F)

Immunogenicity:

- TAb and NAb in CSF; TAb, NAb, total IgE, and drug-specific IgE in serum

Biomarkers:

- Analysis of disease-related biomarkers from CSF and blood

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STATISTICAL METHODS:

A Statistical Analysis Plan (SAP) will be written prior to final database lock that will provide details on the planned statistical analysis. If discrepancies exist between the statistical analysis as described in the protocol and the final SAP, the SAP will prevail.

The primary efficacy endpoint is the 0 to 6-point ML score on the Hamburg CLN2 rating scale. The primary measure of efficacy is the rate of CLN2 decline. This analysis will include patients with a baseline ML score < 6 points and patients with a ML score < 6 points post-baseline. CLN2 disease rating scale scores will be evaluated relative to natural history data in untreated historical controls (data from a CLN2 disease patient registry and data from siblings with CLN2 disease, when available).

Time to disease manifestation will be assessed for asymptomatic patients. For all patients, an analysis of interest is time to first confirmed decline, defined as 2 consecutive CLN2 assessments (i.e., approximately 4 weeks apart) with scores less than the baseline CLN2 score.

Secondary endpoints of key interest include measurements obtained from MRI of the brain, time to disease manifestation (asymptomatic patients), time to first confirmed CLN2 decline (all patients), and the 0 to 12-point total (motor/language/vision/seizure) Hamburg CLN2 scores.

Endpoints will be presented descriptively. Secondary and exploratory endpoints may be compared with natural history data from untreated historical controls (data from a CLN2 disease patient registry and data from siblings with CLN2 disease, when available).

Safety data will be summarized descriptively.

Sample size was determined on the basis of clinical judgment. Statistical power was not a consideration.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AEoSI	adverse event of special interest
BPV	BioMarin Pharmacovigilance
CBC	complete blood count
CFR	Code of Federal Regulations
CLN2	neuronal ceroid lipofuscinosis type 2 disease, also known as classical late infantile CLN2, cLINCL, or Jansky-Bielschowsky disease, a form of Batten Disease
CNS	central nervous system
CRA	clinical research associate
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DRB	Data Review Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
ERT	enzyme replacement therapy
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
ICV	intracerebroventricular
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IT-L	intrathecal lumbar
ITQOL	Infant Toddler Quality of Life Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
ML	Combined score of motor and language subscales on the adapted CLN2 disease rating scale
MRI	magnetic resonance imaging
mUBDRS-Movement	Modified Unified Batten Disease Rating Scale Involuntary Movement Scale

mUBDRS-Seizure	Modified Unified Batten Disease Rating Scale Seizure Inventory
NAb	neutralizing anti-TPP1 antibody
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect-level
OCT	Optical Coherence Tomography
PEDsQL	Pediatric Quality of Life
PEG	percutaneous endoscopic gastrostomy
PLT	Preferential Looking Test
PK	pharmacokinetics
QOL	quality of life
REC	Research Ethics Committee
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verified
SOI	Statement of Investigator
SUSAR	suspected unexpected serious adverse reaction
TAb	total anti-TPP1 antibody
TRE	temporally related events
TPP1	tripeptidyl peptidase-1
UBDRS	Unified Batten Disease Rating Scale
US	United States

5 ETHICS

BioMarin aims to conduct its studies according to the highest scientific standards. The following sections articulate standards to which investigators are held accountable, as well as matters of compliance to document adherence to such standards.

5.1 Ethics Committees

Investigators are expected to interact with ethics committee 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), Independent Ethics Committee (IEC), or Research Ethics Committee (REC) 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/REC will be provided to BioMarin Pharmaceutical Inc. (BioMarin) or its designee.

The principal investigator will provide the IRB/IEC/REC with all appropriate material, including, but not limited to, protocol, Investigator's Brochure (IB), Informed Consent Form (ICF), compensation procedures, and any written information to be provided to study subjects, including all consent forms translated to the native language of the clinical site, or to languages of intended subjects, if they speak a language other than the native language.

The study will be initiated and study drug supplies will be shipped to the site once appropriate documents from the IRB/IEC/REC, confirming unconditional approval of the protocol, ICF, and all subject recruitment materials, are obtained in writing by the principal investigator and copies are received by BioMarin or its designee. Documents approved by the IRB/IEC/REC shall reference the study by protocol title and BioMarin protocol number and include review and approval dates.

BioMarin or its designee will ensure that appropriate study progress reports are made available to the IRB/IEC/REC and BioMarin by the principal investigator in accordance with applicable guidance documents and government regulations.

5.2 Ethical Conduct of Study

It is expected that investigators understand and comply with the letter and spirit of this protocol. This includes and is not limited to establishing and meeting enrollment commitments, including eligible patients in the study, adhering to diagnostic or other procedures as specified in the study, and assuring appropriate compliance with study medication.

This study will be conducted in accordance with the following:

- United States (US) Code of Federal Regulations (CFR) sections that address clinical research studies
- Clinical Trial Directive 2001/20/EC and GCP Directive 2005/28/EC
- Other national and local regulations, as applicable
- ICH E6 R[2], where applicable
- The ethical principles established by the Declaration of Helsinki

Specifically, this study is based on adequately performed laboratory and animal experimentation, will be conducted under a protocol reviewed and approved by an IRB/IEC/REC and will be conducted by scientifically and medically qualified persons. In the opinion of the investigator and BioMarin, the potential benefits of the study outweigh the potential risks. The rights and welfare of subjects will be respected. Each subject, or his/her legally authorized representative, will provide written informed consent before any study-related test or evaluation is performed.

5.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), US 21 CFR §50, Directive 2001/20/EC and applicable local regulations, will be obtained for each subject prior to entering that subject in the study. The investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REC. BioMarin and the IRB/IEC/REC must approve the documents before they are implemented. Copies of the approved ICF and, if applicable, subject information sheet, minor assent form, parental ICF, and all ICFs translated to a language other than the native language of the clinical site, must also be received by BioMarin or its designee prior to any study-specific procedure.

A subject younger than 18 years (or defined as a minor, depending on the region) will provide written assent (if able) 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 to the subject's legally authorized representative) and will maintain the original in the subject's study file.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

The study will be administered 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 Pharmacovigilance (or designee) will be responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities as required.

CSF laboratory evaluations and evaluations of clinical laboratory parameters (blood, urine) will be performed by local study site laboratories. Central laboratories will be used to evaluate TPP1 enzyme activity, genotype, electroencephalograms (EEGs), and magnetic resonance imaging (MRI) scans. Assessment of immunogenicity and exploratory biomarkers will be conducted by BioMarin. Additional details will be provided in the corresponding Study Laboratory Manual.

7 INTRODUCTION

CLN2 disease is a predominantly late infantile form of neuronal ceroid lipofuscinosis and one of the multiple genetic isoforms of Batten Disease. CLN2 is a very rare genetic disease characterized by the deficiency of the lysosomal serine protease TPP1, caused by mutations in the *CLN2* gene. In the absence of TPP1, lysosomal storage materials normally metabolized by this enzyme accumulate as characteristic intracellular deposits in many organs; accumulation in the CNS leads to the neurodegenerative symptoms and, ultimately death. The onset of symptoms is typically between ages 2 and 4 (Chang, 2011); (Kurachi, 2000) with an average age of diagnosis of 4 years (Worgall, 2007). Patients typically present initially with seizures, followed by ataxia, myoclonus, impaired speech, cognitive decline, and developmental regression. A loss of vision follows psychomotor decline, with patients blind and non-ambulatory typically between 6 and 8 years of age. Patients enter into essentially a neurovegetative state during the later stages of the disease and feeding and tending to everyday needs become difficult. Disease progression is rapid with death typically occurring between 10 and 15 years of age.

7.1 Nonclinical Studies

Nonclinical studies support the therapeutic benefit of BMN 190 with acceptable therapeutic index for patients with CLN2 disease. In animal models of CLN2 disease, intracerebroventricular (ICV) or intrathecal lumbar (IT-L) administration of BMN 190 reduced pathologic deposition of storage materials, attenuated cognitive and motor decline, delayed disease progression, and extended lifespan. In TPP-null mice, restoration of TPP1 enzyme activity reduced lysosomal storage accumulation, improved motor function, and extended lifespan (Sleat, 2008); (Xu, 2011). In TPP1-null dogs, BMN 190 also reduced lysosomal storage, preserved function, extended lifespan and delayed clinical signs of neurodegeneration (Vuillemenot, 2011; PI).

BMN 190 concentrations in cerebrospinal fluid (CSF) remained above the lysosomal K_{uptake} for approximately 48 hours after single ICV or IT-L infusions in nonclinical studies (dog and monkey) with CSF dynamics similar to those in human (PI PI). In these same species, CNS distribution of BMN 190 was extensive in many brain regions. Distribution and pharmacokinetics (PK) characteristics after ICV infusion of BMN 190 appear advantageous to IT-L administration for treatment of CLN2 disease. A mean CNS tissue half-life of approximately 2 weeks (range, 3.1 to 87.2 days, depending on CNS site; PI) suggests biweekly dosing will sustain therapeutic BMN 190 levels in the CNS.

Toxicity studies have not identified drug-related adverse effects when BMN 190 is administered by ICV or IT-L infusion to healthy animals or animals with CLN2 disease. Repeated BMN 190 administration was associated with inflammation and neuronal necrosis adjacent to the ventricles and ICV catheter track in dog PI and was largely attributable to the long-term implantation of catheters and related infusion procedures as both untreated and treated animals exhibited the same findings. No findings in any of the nonclinical studies indicate adverse BMN 190-related effects on cardiovascular or central nervous systems. Electrocardiogram (ECG) analysis in cynomolgus monkeys revealed no changes in ECG waveform or heart rate after a single ICV infusion during the time of BMN 190 exposure in the CSF and plasma. Additionally, monthly neurologic and clinical examinations of Dachshunds administered BMN 190 in a repeat-dose studies revealed no clinical CNS signs in Dachshunds attributable to BMN 190 though onset of disease-related neurologic signs was delayed significantly following up to 48 mg BMN 190, compared with vehicle-treated controls. Treatment related safety events were primarily device related or associated with immune response to chronic dosing of heterologous protein. Given the overall tolerability of ICV-delivered BMN190, untoward systemic safety effects were considered unlikely in human.

7.2 Previous Clinical Studies

BMN 190 has been studied in human clinical trials 190-201 and 190-202. Study 190-201 was a 48-week, international, multicenter phase 1/2 open-label dose-escalation study designed to assess the safety and efficacy of BMN 190 administered to patients with mild to moderate CLN2 disease by direct intracerebroventricular infusion to the CNS; Study 190-202 is the open-label extension of 190-201. These studies evaluated the safety, tolerability and efficacy of BMN 190 given as an infusion of 300 mg every 14 days given directly to the CNS using a permanently implanted intracerebroventricular (ICV) access device. A total of 24 patients with screening CLN2 motor-language scores ≥ 3 (0 to 6 point scale) and age ≥ 3 were enrolled into the 190-201 study. All completers without predefined stopping criteria were qualified to enroll into the long term extension, Study 190-202.

All patients had successful surgical implantation of ICV access devices, with device complication rates consistent with what has been observed in the published literature.

Interim results of the completed 48-week open-label study (190-201) and the ongoing extension study (190-202) have been published (Schulz, 2018). The primary outcome measure was the time until a 2-point decline in the score on the motor and language domains of the CLN2 Clinical Rating Scale (which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains), which was compared with

the time until a 2-point decline in 42 historical controls. Additionally, rate of decline in motor–language score was compared between the two groups using data from baseline to the last assessment with a score of more than 0, divided by the length of follow-up (in units of 48 weeks).

Twenty-four subjects were enrolled in Study 190-201/190-202, 23 of whom constituted the efficacy population. Interim efficacy results demonstrated a statistically significant and durable treatment effect in attenuating disease progression as measured by CLN2 scores and in comparison to natural history. Of the 24 patients enrolled into Study190-201, all but 2 subjects were in the active loss of function phase of the disease characterized by both notable disease burden and decline by a median value of 2 points per 48 weeks. In the 23 subjects who received BMN 190 for at least 96 weeks in Study 190-201/ 190-202, the median time until a 2-point decline in the motor–language score was not reached and was 345 days for historical controls. The mean (SD) unadjusted rate of decline in the motor–language score per 48-week period was 0.27 (0.35) points in treated subjects and 2.12 (0.98) points in 42 historical controls (mean difference, 1.85; $P < 0.001$). Common AEs included convulsions, pyrexia, vomiting, hypersensitivity reactions, and failure of the intraventricular device. In 2 subjects, infections developed in the intraventricular device that was used to administer the infusion, which required antibiotic treatment and device replacement.

PK analysis of ICV-delivered BMN 190 demonstrates concentrations and exposures that are three orders of magnitude greater in the CSF than in the plasma.

No association was found between ADA, including drug-specific IgE positivity, and incidence or severity of hypersensitivity adverse events.

Taken together, the response in the treated group is significant when compared to the loss of function predicted by natural history studies. The conclusions of treatment effect are constant across all analysis methodologies and sensitivity analyses. Most patients (87%) experience neurodegenerative stabilization, in which active decline in function is either halted (57%), has an early single point decline with no subsequent loss (22%) or actually improves function on treatment (9%).

In conclusion, BMN 190 via ICV infusion is generally safe and well tolerated. BMN 190 treatment demonstrated a durable and clinically meaningful therapeutic effect on attenuating disease progression compared to natural history.

7.3 Study Rationale

BMN 190 is a recombinant form of human TPP1, the enzyme deficient in patients with CLN2 disease. As enzyme replacement therapy (ERT), BMN 190 is expected to restore

TPP1 enzyme activity in the brain and alter neurological disease progression. Given the urgent and severe unmet medical need in CLN2 disease and observations of safety and efficacy in neurologically relevant animal models of CLN2 disease, clinical development of BMN 190 ERT is justified.

Murine and canine models of CLN2 disease (sharing the same genetic and enzymatic defect, TPP1 deficiency, as the human disorder) recapitulate the major human clinical signs and pathology, including neuron loss, tremor, ataxia, functional decline, and reduced lifespan (Awano, 2006); (Sleat, 2004). ERT with BMN 190 administered intrathecally in both models yielded pharmacologically significant benefit. Furthermore, when dosing started early in life (~2.5 months of age) in the TPP1-null dachshund model, BMN 190 significantly delayed onset of clinical signs, preserved motor and cognitive function, and prolonged life. The better pharmacological response to ERT in this and other animal models, when treatment was started closer to birth, indicates the importance of starting therapy as early in life as possible (Dierenfeld, 2010).

The relationship of the start of therapy to overall clinical response will be evaluated in pediatric patients (from birth to < 18 years of age) with CLN2 disease treated with BMN 190 compared to natural history data from untreated historical controls (data from a CLN2 disease patient registry and data from siblings with CLN2 disease, when available). The comparison of treatment with untreated controls will occur from the time of the initiation of study drug.

7.4 Overall Risks and Benefits

Nonclinical toxicity studies have not identified drug-related adverse effects associated with chronic ICV administration of BMN 190 to healthy or CLN2 animal models disease.

BMN 190 has been studied in 24 patients in 5 clinical sites for Studies 190-201 and 190-202. The current clinical experience in human clinical trials demonstrates an acceptable benefit-risk profile to both the placement and chronic use of ICV access devices, and to infusion of BMN 190 at 300 mg every 14 days as demonstrated by interim efficacy and safety results summarized in Section 7.2. The efficacy objective of this study is to prevent patients from entering into the active rapid loss of function phase of the disease, or to attenuate further progression of disease. Monitoring and evaluation of specific adverse events of hypersensitivity reactions and device-related complications are discussed in Sections 7.4.1 and 7.4.2. Given the severity of disease, clinical and nonclinical support, the overall risks and benefits support this protocol.

7.4.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and less severe allergic reactions, are an identified risk for ERT in general, including BMN 190. Thus, anaphylaxis and less severe allergic reactions may occur during and following ICV infusion of BMN 190. Therefore, it is required that appropriately trained personnel and equipment for emergency resuscitation (including epinephrine) be available near the bedside during study drug infusion. For information regarding the reporting of hypersensitivity reactions, refer to Section 10.4.1.

An allergic reaction is a disorder characterized by an adverse local or general response from exposure to an allergen. Allergic reaction may include a combination of the following symptoms: flushing or rash, fever, urticaria, dyspnea, symptomatic bronchospasm with or without urticaria, allergy-related edema/angioedema, hypotension, or anaphylaxis. Infusion of BMN 190 may provoke additional symptoms of allergic reactions not included in this list. The investigator will categorize the severity of an allergic reaction as described in Section 10.2.3.2.

Anaphylaxis, a systemic, immediate hypersensitivity reaction, is the most severe form of hypersensitivity reaction. Symptoms may occur during or within hours following infusion of an agent and, generally, more rapid onset indicates more severe reaction; death may result. Managing anaphylaxis requires early recognition of signs and symptoms and clinicians well trained in the management of acute events. Symptoms of anaphylaxis may include involvement of skin and/or mucosal tissue (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia), and reduced blood pressure or end-organ dysfunction (e.g., hypotonia, syncope, incontinence).

All AEs, including hypersensitivity, anaphylaxis and other allergic reactions that occur within 24 hours after infusion start or restart, regardless of the investigator's assessment of study drug relationship, will be considered to be temporally related events (TREs). It is expected that the TREs of greatest clinical importance will be hypersensitivity reactions, but not all TREs may be allergic in nature. The risk of such reactions may be mitigated by specific measures, including pretreatment or infusion modification, as described in Section 9.4.4.

7.4.2 Risks of Intracerebroventricular Devices and Drug Administration

Patients in this study will be required to have an ICV reservoir surgically implanted for administration of BMN 190. An MRI will be performed in advance of the procedure to ensure proper planning and placement of the ICV access device. The ICV access device

placement procedure will be performed under general anesthesia by qualified surgeons and will include placement of an endotracheal breathing tube during the procedure. Patients will be monitored closely in a nursing-intensive environment for 48 hours post-ICV device placement and after the start of the first drug infusion. Following ICV access device placement, subjects and their caregivers will be given written instructions providing details on signs and symptoms of concern for device complications and instruction on when to return to the site for device evaluation. An additional follow-up phone call will be conducted within 48 hours of inpatient discharge for all visits.

Risks associated with the procedure include sore throat, hoarseness, mouth pain, injury to the mouth or teeth, injury to blood vessels, aspiration and pneumonia. Although rare, unexpected severe complications with anesthesia can occur and include the possibility of infection, bleeding, drug reactions, blood clots, loss of sensation, loss of limb function, paralysis, stroke, brain damage, heart attack, or death.

Common side effects after the procedure include nausea, vomiting, dry mouth, sore throat, shivering, sleepiness, mild hoarseness, and pain.

The ICV access device will be available for first infusion ≥ 14 days after placement. First dose must take place within 28 days of placement.

The use of ICV access devices can result in infections, intracerebral hemorrhage, reservoir leakage, and seizures (Karavelis, 1996), (Kronenberg, 1998). Additional surgery may be required to fix or replace the devices. The technical complication rate of one ICV reservoir study in 106 cancer patients was 10.3% with almost half of these complications requiring surgical revision (median time reservoirs were in place was 4.1 months ranging from 2 days to 4.6 years) (Lishner, 1990). The current complication rate for BMN 190 administration is consistent with this large series report.

Patients will be monitored throughout the study for potential infections (high temperature, cough, rash, headache, mental status changes, swelling or drainage in the incision area) and signs of ICV reservoir leakage or failure (refer to Section 9.7.5.2). Material degradation of the ICV device reservoir has occurred after approximately 105 perforations of the ICV device in benchtop testing, and has been observed in clinical trials with approximately 4 years of BMN 190 administration. Access device replacement should be considered prior to 4 years of regular administration of Brineura; with the decision made on an individual subject level based on the medical judgment of the Investigator. The CSF will be monitored for signs of infection at each infusion. If a device infection is confirmed, the site will confer with the sponsor and neurosurgical support to manage the intervention including potential device

removal, treatment with appropriate antimicrobial medications, and the suitability and timing of replacement and re-initiation of therapy.

All BMN 190 infusions are given in an inpatient setting with supportive measures present. For all infusions, patients will be monitored in an appropriate inpatient setting for a minimum of 24 hours from the start of the infusion. For the first infusion only, subjects will also return for a follow-up visit to clinic 72 hours (and no later than the third calendar day) after the start of infusion. After all visits, the parent or legal guardian will be telephoned within 48 hours to determine health status.

8 STUDY OBJECTIVES

The primary objectives of this study include the following:

- evaluate safety and tolerability of BMN 190 administered via intracerebroventricular (ICV) device
- to evaluate treatment effectiveness as a delay in progression of motor-language (ML) score on the Hamburg CLN2 clinical rating scale
- assess immunogenicity of BMN 190 in CSF and serum

Secondary objectives of this study include the following:

- to characterize the pharmacokinetics of BMN 190 in CSF and plasma
- measure MRI parameters of disease progression
- assess impact of treatment on the total Hamburg clinical rating scale
- assess the time to disease manifestation for asymptomatic patients

Exploratory objectives of this study include the following:

- assess development achievement
- assess abnormal involuntary movements
- evaluate retinal anatomy using optical coherence tomography (OCT)
- determine seizure onset, type and frequency
- determine change in seizure activity
- anti-epileptic treatment
- assess quality of life metrics
- assess changes in EEG
- assess changes in visual acuity
- analysis of disease-related biomarkers from CSF and blood

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This will be a Phase 2 open-label, multicenter study in pediatric patients < 18 years of age with CLN2 disease, confirmed by deficiency of TPP1 enzyme activity and mutation of the CLN2 gene. The study is designed to assess disease progression in CLN2 patients treated with BMN 190 compared to natural history data from untreated historical controls (data from a CLN2 disease patient registry and data from siblings with CLN2 disease, when available). The comparison of treatment with untreated controls will be compared from the time of the initiation of study drug. A summary of events is provided by visit in Table 9.1.1

The planned enrollment for this study is at least 10 patients: at least 5 patients with a Hamburg ML score ≥ 5 points, at least 5 patients with a ML score < 5 points, and at least 5 patients < 2 years of age. Study eligibility will be determined and enrollment will occur before (≤ 21 days) subjects are admitted to the hospital for surgical implantation of an ICV access device. The Baseline visit to collect clinical scores and clinical laboratory parameters will be completed no more than 2 days before the first infusion.

BMN 190 will be administered every 14 days from the date of the first infusion (±3 days) for at least 144 weeks according to the patient's age:

- birth to < 6 months: 100 mg
- 6 months to < 1 year: 150 mg
- 1 year to < 2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- ≥2 years: 300 mg

Patients younger than 2 years will start the study at the dose level appropriate for their age and will transition to the dose level consistent with their age as they mature. Upon study completion or early termination, all patients will be given the opportunity to participate in a postmarketing registry that will assess the long-term safety and efficacy of BMN 190 for patients receiving commercial drug.

Patients in this study will be required to have an ICV reservoir surgically implanted for administration of BMN 190. An MRI will be performed in advance of the procedure to ensure proper planning and placement of the ICV access device. Patients will be monitored closely in a nursing-intensive environment for 48 hours post-ICV device placement and after the start of the first drug infusion. Following ICV access device placement, subjects and their caregivers will be given written instructions providing details on signs and symptoms of concern for device complications and instruction on when to return to the site for device

evaluation. These instructions should be provided by the institution and be based on local standard of care. An additional follow-up phone call will be conducted within 48 hours of inpatient discharge for all visits.

The first infusion will occur at least 14 days from surgery to implant the ICV reservoir and no more than 28 days after surgery. In the event that the ICV device is replaced, the next infusion will occur at least 14 days and no more than 28 days after surgery. All removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and all other devices (as described in the Pharmacy Manual) except for infusion pumps, should also be returned. Age-specific dosing will be initiated every 14 days (±3 days) from the date of the first infusion.

The normal infusion will be administered over 4 (±1) hours at a rate of 2.5 mL/hr; the dose will be determined by the patient's age. Subjects not receiving the full 300 mg dose (administered in a total volume of 10 mL) will receive the appropriate volume at a rate of 2.5 mL/hr for over a shorter duration of time (See Section 9.4.1).

Dosing can be adjusted in the judgement of the investigator, upon consultation with the medical monitor, to manage AEs as outlined in Table 9.4.1.1. Should the dose-limiting AE resolve in the opinion of the investigator, and upon consultation with the medical monitor, dosing at the full dose may resume.

In patients younger than 2 years, dosing may also be adjusted by the sponsor in consultation with the investigator and medical monitor based on results from PK analysis, as follows:

- Within a patient, if the observed CSF AUC_{0-t} exceed the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be reduced to 50% of the recommended age-appropriate dose.
- Within a patient, if the observed CSF AUC_{0-t} is less than the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be increased to the recommended dose for the next oldest age group.

Infusions will be performed in a 4-hour period (±1 hr). Generally, functional and QOL assessment should precede MRI and sampling, which should precede infusion; sample collection may occur when subjects are sedated for MRI. If a subject is discontinued from the study prematurely, an Early Termination visit should be scheduled within 3 days.

For all infusions, subjects will be monitored in an appropriate inpatient setting for a minimum of 24 hours from the start of the infusion. For the first infusion only, subjects will also return for a follow-up visit to clinic 72 hours (and no later than the third calendar day) after the start of infusion. After all visits, the parent or legal guardian will be telephoned within 48 hours to determine health status.

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, respiration rate, and temperature) will be measured within 30 (±5) minutes before infusion start (or restart), every 30 (±5) minutes during infusion, 0.5 hours (±5 minutes), 1 hour (±5 minutes), and 4 hours (±15 minutes) after infusion end, and then every 4 hours (±15 minutes) for the next 16 hours. Blood pressure will be measured in the upper arm using an appropriately sized blood pressure cuff. If the patient's blood pressure is abnormal (as compared to site-specific reference ranges), a manual blood pressure will be obtained by a trained healthcare professional.

For the first infusion of BMN 190, continuous ECG monitoring (3- or 5-lead) will be performed for all subjects. The ECG should begin 15 (± 5 minutes) prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. In the event that the subject has already received the first infusion of BMN 190, the next infusion will be monitored as above. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG.

A standard ECG (12-lead), including heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities, will be performed 30 (±5) minutes after infusion end at the first infusion and every 24 weeks thereafter. In patients with present or past bradycardia, conduction disorders, or with structural heart disease, an ECG will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, 30 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end for each study drug infusion.

Efficacy will be measured using the 0 to 6-point ML score on the Hamburg CLN2 rating scale as the primary endpoint. The 12-point total score (motor, language, vision, and seizure subscales) on the Hamburg CLN2 scale and MRI measures of disease progression will be collected as secondary endpoints. Exploratory efficacy measures will include developmental status, involuntary movements, retinal anatomy using OCT, seizure frequency, change in seizure activity (as measured by Hamburg score), seizure frequency, change in seizure activity (as measured by Hamburg score), anti-epileptic treatment, quality of life metrics, changes in EEG, assessment of visual acuity, and analysis of disease-related biomarkers. The safety and tolerability of treatment will be assessed by collection of AEs, physical findings, vital signs, ECGs, and clinical laboratory tests. AEs will be assessed by the investigator for severity, seriousness, and relationship to study drug and/or the ICV access device.

Because hypersensitivity reactions may be associated with ERT administration, subjects should be pretreated with an age-appropriate dose of antihistamine (and antipyretic, if

appropriate) medication approximately 30 minutes (± 15 minutes) before infusion. Subjects may be pretreated, at the discretion of the Investigator, with age-appropriate sedative medication approximately 30 minutes (± 15 minutes) before BMN 190 infusion according to institution's standard practices.

A temporal relationship to study drug infusion will be utilized to define TREs. This should be distinguished from the clinical assessment of an infusion reaction. Thus, an AE occurring within 24 hours of the start or restart of BMN 190 infusion will be defined as a TRE.

Some of the events that occur within the 24 hour period post-infusion may be hypersensitivity mediated. Hypersensitivity reactions are characterized by an adverse local or general response from exposure to an allergen. Symptoms of hypersensitivity reactions may include fever, chills/rigors, skin symptoms (urticaria, angioedema, rash), respiratory symptoms (dyspnea, wheezing, stridor), gastrointestinal symptoms (nausea, vomiting, abdominal pain) and/or cardiovascular changes (hypotension/hypertension).

In severe cases, anaphylaxis – a systemic hypersensitivity reaction – may also occur. Anaphylaxis is the most severe form of hypersensitivity reaction in which symptoms may occur during or within hours of an infusion; if anaphylaxis goes untreated, death may result. Symptoms of anaphylaxis may include involvement of skin and/or mucosal tissue (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia), and reduced blood pressure or end-organ dysfunction (e.g., hypotonia, syncope, incontinence).

To date there has been no anaphylaxis or anaphylactoid reactions in studies with BMN 190. However, in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or severe hypersensitivity (defined as a hypersensitivity event of Grade 3 or higher), blood samples to assess C4, serum tryptase, and total IgE will be collected within 1 hour of the event and tested; a blood sample to assess drug-specific IgE will be collected no sooner than 8 hours after the event (or before the next infusion).

In addition, the investigator must contact the BioMarin medical monitor (Section 10.8) within 1 business day if any AE is severe (Grade 3 or higher) or serious and requires any of the following:

- infusion interruption, discontinuation, or modification (not due to blocked line)
- administration of IV fluids, steroids, or antihistamines
- administration of oxygen

Before subsequent infusions, the investigator and BioMarin medical monitor will discuss the case and agree upon infusion modification or additional premedication. Agreed upon dose modifications or introduction of additional premedication should be documented in the Case Report Forms and source files.

Another possible AE is infection from the indwelling ICV catheter. If an infection is suspected, blood and CSF samples will be drawn for assessments. The subsequent course of therapy may include antibiotic therapy and catheter reposition or withdrawal. If BMN 190 treatment is suspended, BMN 190 may resume if no more than 4 consecutive missed doses elapse after the last given dose.

A schedule of planned assessments during the study is provided in Table 9.1.1.

Table 9.1.1: Schedule of Events

Assessments and Events	Screening[a]		Baseline/First Infusion		Treatment Period Weeks 1 to 144	Study Completion / Early Termination	Device Safety Follow-Up	Safety Follow-Up
	≤ 21 days prior to ICV Surgery		≤2 Days prior to first dose	First Infusion Visit (Days 1-6)	Visit every 2 weeks (±3 days)	Proximity to last dose (+3 days)	4 weeks after device removal (±3 days)	6 months after last dose ±1week
Informed consent/assent[a]	X	ICV Surgery and Recovery (14-28 days) [k]						
CLN2 Genotype[b]	X[b]							
Blood for TPP1 Activity and CLN2 gene analysis [b]	X							
CLN2 disease rating scale[c]	X		X		Q4W	X	X	X
Videotaping (CLN2 disease rating scale)[c]	X		X		Q12W	X		
Verify criteria for study entry	X							
ECG, 3- or 5-lead[d]				X[d]				
ECG, 12-lead[e]			X	X	Q24W	X		X
EEG, standard awake[f]			X		Q24W	X		
Cranial MRI[g]	X		X		Q24W	X		
CSF (cell count, protein, glucose, and culture)[h]				D1, D6	Q2W	X		
Device patency/infection[i]				D1, D6	Q2W			
Administer study drug[j]				D1	Q2W			
Phone follow-up[k]					Within 48 hours after inpatient discharge each visit[k]			
CSF / plasma for PK[l]				D1	Q24W	X		
CSF / blood for disease-related biomarkers[m]				D1	CSF: Q2W (Wks 1-71), Q8W	X		

Assessments and Events	Screening[a]		Baseline/First Infusion		Treatment Period Weeks 1 to 144	Study Completion / Early Termination	Device Safety Follow-Up	Safety Follow-Up
	≤ 21 days prior to ICV Surgery		≤2 Days prior to first dose	First Infusion Visit (Days 1-6)	Visit every 2 weeks (±3 days)	Proximity to last dose (+3 days)	4 weeks after device removal (±3 days)	6 months after last dose ±1week
					(Wks 79-145) Blood: Q8W (Wks 1-49), Q12W (Wks 61-145)			
CSF/serum for immunogenicity[n]			X	Q12W		X	X (serum only)	X (serum only)
Vital signs[o]				D1	Q2W	X	X	X
Complete physical examination[p]	X		X		Q48W	X		X
Brief physical examination[p]				D1, D6	Q2W		X	
Height and weight assessments			X		Q24W	X		X
Neurological examination[p]			X		Q12W	X	X	
Blood/urine for clinical lab tests[q]			X	D2	Q4W x 2 (Wks 1-9), then Q8W x 5 (Wks 17-49), then Q12W (Wks 61-145)	X	X	X
Modified Unified Batten Disease Rating Scale Involuntary Movement Scale			X		Q12W			
Modified Unified Batten Disease Rating Scale Seizure Inventory			X		Q12W			
Optical coherence tomography[r]			X		Q24W	X		

Assessments and Events	Screening[a]		Baseline/First Infusion		Treatment Period Weeks 1 to 144	Study Completion / Early Termination	Device Safety Follow-Up	Safety Follow-Up
	≤ 21 days prior to ICV Surgery		≤2 Days prior to first dose	First Infusion Visit (Days 1-6)	Visit every 2 weeks (±3 days)	Proximity to last dose (+3 days)	4 weeks after device removal (±3 days)	6 months after last dose ±1week
PedsQL[s]			X		Q12W	X		
Denver II Developmental Scale[t]			X		Q12W	X		
CLN2-specific QoL questionnaire[s]	X		X		Q12W	X		
Ophthalmologic assessments			X		Q48W	X		
Visual acuity testing[u]			X		Q12W	X		
Pregnancy testing (in females of childbearing potential)[v]	X					X		
Adverse events, including ongoing seizure history[w]	X		Continuous monitoring					
Prior and concomitant medications, including anti-epileptic treatments[x]	X		Continuous monitoring					
Hypersensitivity Labs[y]			As needed, only in the event of suspected anaphylactic reaction, serious or severe hypersensitivity[y]					
ICV Device Removal[z]						X[z]		

Baseline values will be recorded no more than two days before the first infusion, which will occur at least 14 days from surgery and no more than 28 days after surgery. Thereafter, study visits will be every 2 weeks ±3 days from the date of the first infusion. If a subject is discontinued from the study prematurely, an Early Termination visit should be scheduled within 3 days.

[a] Written informed consent must be obtained before study procedures begin. All screening procedures are to be completed ≤21 days prior to the ICV implant surgery. Sponsor approval must be obtained prior to ICV implant surgery.

[b] Diagnosis of CLN2 disease determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at Screening. In addition, blood for TPP1 enzyme activity and CLN2 gene analysis will be collected to be analyzed centrally.

[c] Two domains (motor and language) of the Hamburg CLN2 disease rating scale will be tested at Screening (entry criterion). All 4 domains (motor, language, vision, and seizure) of the Hamburg CLN2 scale will be tested at Baseline visit prior to first infusion, every 4 weeks during the treatment period, at Early Termination/ Study Completion visit, at the 4-week Device

Safety follow-up, and at the 6-month Safety follow-up visit. CLN2 rating scale evaluations will be videotaped every 12 weeks, and at the Early Termination/ Study Completion Visit. CLN2 assessments should precede MRI and blood and CSF sampling.

[d] For the first infusion of BMN 190, continuous ECG monitoring (3- or 5-lead) will be performed for all subjects. The ECG should begin 15 (± 5 minutes) prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. In the event that the subject has already received the first infusion of BMN 190, the next infusion will be monitored as above. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG.

[e] A standard ECG (12-lead), including heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities, will be recorded. ECG will be performed 30 (±5) minutes after infusion end at the first infusion and every 24 weeks thereafter. In patients with present or past bradycardia, conduction disorders, or with structural heart disease, an ECG will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, 30 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end.

[f] At each timepoint, a standard awake electroencephalogram (EEG) will be recorded within 2 days before infusion.

[g] The Screening Cranial MRI will be performed prior to surgery to ensure proper planning and placement of the ICV access device. MRI should precede blood and CSF sampling. A ±4-week window is allowed for this assessment and the scan may be performed at the same time as a scheduled infusion.

[h] CSF (for cell count with differential, protein, glucose, and culture) will be collected within 30 (±5) minutes before every infusion (or within 1 week of the Early Termination visit). During the first infusion, CSF (for cell count, protein, glucose, and culture) will be collected within 30 (±5) minutes before the infusion (Day 1).

[i] Device and surgical location of the device should be observed prior to each infusion for any swelling or signs of infection of the scalp or surrounding area.

[j] Because hypersensitivity reactions may be associated with ERT administration, subjects should be pretreated with age-appropriate doses of antihistamine (and antipyretic, if appropriate) medication approximately 30 minutes (± 15 minutes) before BMN 190 infusions.

[k] Subjects will be monitored in a nursing-intensive setting for a minimum of 48 hours post-ICV device placement and after the start of the first drug infusion. Following ICV access device placement, subjects and their caregivers will be given written instructions providing details on signs and symptoms of concern for device complications and instruction on when to return to the site for device evaluation. An additional follow-up telephone call will be conducted within 48 hours after inpatient discharge for all visits.

[l] Samples of CSF and plasma for PK analysis will be collected within 15 minutes before infusion start, and 0.25, 4, 8, 20 (±5 minutes), 72, and 120 (±15 minutes) hours after infusion end. Samples will be collected on Day 1, and Weeks 25, 49, and 97. There will be no PK samples collected at Week 73 or after Week 97.

[m] Samples of blood and CSF will be collected prior to infusion. Collection of CSF will be every 2 weeks from Weeks 1 to 71 and every 8 weeks from Weeks 79 to 145; blood will be collected every 8 weeks from Weeks 1 to 49 and every 12 weeks from Weeks 61 to 145.

[n] Samples of blood (serum) and CSF will be collected for TAb and NAb testing before the first infusion (Baseline or Week 1 before the infusion), every 12 weeks thereafter, and at the Study Completion Visit. Samples of blood (serum) will be collected for TAb testing at the Device Safety Follow-Up and Safety Follow-Up visits (or within 1 week of the Early Termination visit). Collection must precede infusion. NAb will be tested at baseline and at subsequent time points when TAb is positive. Samples of blood (serum) will be collected to assess baseline total and drug-specific IgE levels in the event of later hypersensitivity reactions requiring additional lab work (as outlined in note x below).

[o] Vital signs (SBP, DBP, heart rate, respiration rate, and temperature) will be measured within 30 (±5) minutes before infusion start (or restart), every 30 (±5) minutes during infusion, 0.5 hours (±5 minutes), 1 hour (±5 minutes), and 4 hours (±15 minutes) after infusion end, and then every 4 hours (±15 minutes) for the next 16 hours. Blood pressure will be measured in the upper arm using an appropriately sized blood pressure cuff. If the patient's blood pressure is abnormal (as compared to site-specific reference ranges), a manual blood pressure will be obtained by a trained healthcare professional.

[p] Details on complete and brief physical examinations and neurological examination are provided in Section 9.7.5.

[q] Collection of samples for clinical laboratory assessments should precede infusion. Collection will be every 4 weeks for 2 assessments (Weeks 1-9), every 8 weeks for 5 assessments (Weeks 17-49), and then continue at a frequency of every 12 weeks thereafter (Weeks 61-145).

[r] OCT should precede infusions. In order to limit the need for sedation to perform this assessment, measurement should be obtained while the subject is also under sedation for MRI acquisition.

[s] Quality of life will be assessed using the PedsQL (including both a Parent Report for Toddlers and a Family Impact Module) and a CLN2 disease-based QoL instrument. If done on the same day, assessment of QOL should precede MRI, infusion, and other procedures. PedsQL parent report for appropriate age of subject.

[t] If done on the same day, assessment of the Denver II Scale should precede MRI and sampling.

[u] All subjects will undergo Preferential Looking Testing every 12 weeks. In addition, for those children who retain the cognitive function to adhere to testing, the Lea Vision Test or E Hook (or Tumbling E) Vision Test should also be performed during the same assessment. Visual acuity testing can be performed either before or after the infusion (± 3 days), but should be performed at a time (relative to infusion) that can be repeated consistently between study visits. The subject must not be sedated at the time of visual acuity testing.

[v] Pregnancy in a patient or partner should be reported within 24 hours of the site becoming aware of the pregnancy and will continue through 6 months after the last dose of study drug. Refer to Section 10.3.1.10 for further information.

[w] From signed ICF to first dose of study drug only SAEs related to study mandated procedures are reported. From implantation of ICV device all devices related events are reported. All AEs and SAEs will be recorded starting with the first dose of study drug in Study 190-203 until 6 months after either the last administration of study drug or the Early Termination visit. A Safety Follow-Up visit will also be performed within 6 months after the last administration of study drug or Early Termination. The 6-month Safety Follow-Up Visit will be waived for subjects who begin receiving study drug in another BioMarin-sponsored study or registry within this 6-month period. For subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week Device Safety and 6-month Safety follow-up visit will capture information regarding ongoing events at the time of the last dose or new events related to study drug.

[x] Medications (prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days before informed consent will be recorded in the eCRF at Screening. At each subsequent visit (or within 1 week of the Early Termination visit), change in any medication (dosage, frequency, new medication, or cessation) since the previous visit will be recorded in the eCRF. Any concomitant medication added or discontinued during the study should be recorded in the eCRF (or within 1 week of the Early Termination visit). Subjects may be taking anticonvulsants and medications for myoclonus, tremor, agitation, and pain. Investigators will be asked to keep these regimens constant throughout the study, unless changes are required due to lack of efficacy or toxicity. Use of non-drug therapies such as physical and occupational therapy should also be noted in the eCRF.

[y] In the event of a suspected anaphylactic reaction, serious hypersensitivity event, or severe hypersensitivity (defined as a hypersensitivity event of Grade 3 or higher), blood samples to assess C4,serum tryptase, and total IgE will be collected within 1 hour of the event and tested; a blood sample to assess drug-specific IgE will be collected no sooner than 8 hours after the event (or before the next infusion).

[z] Following either the study completion visit (Week 145) or the Early Termination Visit, arrangements should be made for removal of the ICV access device. All removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and all other devices (as described in the Pharmacy Manual) except for infusion pumps, should also be returned. If the subject intends to continue to receive BMN 190 following participation in this study (e.g., via commercial product, use in a registry, or another BMN 190 study), then the device does not need to be removed. Device removal should occur no more than 4 weeks after the last administration of study drug. A device removal safety follow-up visit will be performed within 4 weeks (± 3 days) from removal of the ICV access device.

9.1.1 Screening

Before any study-related procedure is performed, parents or legal guardians will provide informed consent for study-eligible patients. Patients will be assessed to determine whether they meet study entry criteria (Section 9.3) and are suitable candidates for implantation of an ICV access device. The diagnosis of CLN2 disease is determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at Screening. In addition, blood for TPP1 enzyme activity and CLN2 gene analysis will be collected to be analyzed centrally. Screening procedures are to be completed ≤ 21 days prior to the ICV reservoir implant surgery.

CLN2 rating scales will be performed in full (Appendix 1). Study entry will require a 2-domain ML score of 3-6, as defined in the Ratings Assessment Guideline. The Ratings Assessment Guidelines provide detailed instructions on rating scale assessment, and the Imaging Charter provides instructions on MRI evaluation by a centralized facility. In addition, a complete physical examination will be conducted.

In order to ensure appropriate patients are enrolled in the study (including those with the necessary CLN2 ML scores at Screening), a confirmation of patient study eligibility will be provided to the Investigator by BioMarin. Surgery should not be performed until this approval is obtained. Information that must be provided for Sponsor approval includes (but is not limited to) patient age, results of TPP1 enzyme activity, results of CLN2 genotype testing (if available) and Screening ML score.

9.1.2 Surgery and First Dose

Study subjects will be admitted to the hospital for surgical implantation of an MRI-compatible ICV access device in the lateral ventricle of the right hemisphere; surgery and anesthesia will be under the direction of a neurosurgeon (refer to Study Pharmacy Manual for compatible ICV reservoirs and cannula). An MRI will be performed prior to the surgery to ensure proper planning and placement of the ICV access device. Generally, surgery and postoperative care will be determined by standards of care at the study centers and specific clinical needs of the subject. Subjects will be monitored in a nursing-intensive setting for a minimum of 48 hours post-ICV device placement and after the start of the first drug infusion. Following ICV access device placement, subjects and their caregivers will be given written instructions providing details on signs and symptoms of concern for device complications and instruction on when to return to the site for device evaluation.
An additional follow-up telephone call will be conducted within 48 hours after inpatient discharge for all visits.

The first infusion will occur at least 14 days from surgery to implant the ICV reservoir and no more than 28 days after surgery. In the event that the ICV device is replaced, the next infusion will occur at least 14 days and no more than 28 days after surgery. At the first (and each subsequent) study drug administration, the investigator will evaluate the patency, location, and skin integrity of the reservoir. Access to the device is performed using strict sterile technique. Skin covering the reservoir is inspected for an appropriate needle insertion site. The needle insertion site must be intact, without evidence of breakdown, wound, infection or rash. The needle used is a small gauge non-boring tip. Once the reservoir has been accessed, the needle is immobilized to ensure minimal movement or risk of removal. If the needle dislodges during an infusion, it may not be reinserted, as sterility has been compromised. Guidance for assessing the reservoir devices for leakage and replacement is provided in the Study Pharmacy Manual. At the discretion of the investigator and/or neurosurgeon, the reservoir may be replaced during the clinical study.

9.2 Discussion of Study Design, including Choice of Control Group

This study must be performed in patients with CLN2 disease because neither ICV access device implantation nor potential development of TPP1 autoimmunity, and their unknown long-term health consequences, are acceptable risks for healthy volunteers. However, these risks in a patient population are balanced by the near certainty of severe disability and death within a few years.

The diagnosis of CLN2 disease determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at Screening. In addition, blood for TPP1 enzyme activity and CLN2 gene analysis will be collected to be analyzed centrally.

Because CLN2 disease is fatal in childhood, the study population must be children. Because therapeutic benefit is unlikely in advanced CLN2 disease, given the extensive depletion of cortical neurons, lack of extensive CLN2 disease progression is required for study participation, resulting in a study population comparable to that of a TPP1 gene therapy study (Worgall, 2008). Safety evaluation would also be limited in advanced patients, who are essentially in a vegetative state.

A clinical rating scale, the Hamburg Scale, was developed to document the natural history of CLN2 disease (Steinfeld, 2002). A modified form of that scale, the Modified Hamburg Scale, demonstrated statistically significant slowing of neurologic decline in subjects receiving gene therapy intervention when compared with decline among control subjects (Worgall, 2008). A second CLN2 disease rating scale, the Weill Cornell Scale (Dyke, 2012); (Worgall, 2007), has also been used to evaluate CLN2 disease severity with highly comparable results.

Although all 4 domains of the Hamburg rating scale will be completed (Appendix 1), the motor and language domains are most useful for this study. Language and motor are the earliest domains to lose function, therefore the aggregate CLN2 motor-language scale are appropriate metrics for screening and efficacy. To be eligible for study participation, motor and language domains administered during Screening must document CLN2 disease progression with a 2-domain ML score of 3-6 for these 2 domains, as defined in the Ratings Assessment Guideline. The planned patient enrollment of at least 10 patients is to include at least 5 patients with a combined ML score ≥ 5 points (mild disease) and at least 5 patients with a ML score < 5 points (moderate disease) to ensure that an equal number of patients with mild and moderate disease are enrolled. In addition, at least 5 patients < 2 years of age will be enrolled. The effectiveness endpoint will compare motor and language subscale scores of treated study subjects with those of untreated patients acquired from the natural history data of CLN2 disease registries and data from siblings with CLN2 disease, when available.

The remaining 2 domains in the rating scale (Appendix 1) are less likely to be informative for this study. In order to capture the seizure and movement disorder manifestations of CLN2 disease in more detail, adapted domains from the Unified Batten Disease Rating Scale (UBDRS) are incorporated into the protocol. The UBDRS domains record involuntary movements and seizures according to type, frequency and severity (Kwon, 2011).

Because of practical (limited number of available patients) and ethical (neurosurgery in children with fatal neurologic disease) concerns, this study design cannot involve contemporaneous, matched, randomized, blinded, or untreated control subjects (Arkin, 2005); (Crystal, 2004.). Motor and language subscales and total scores for the Hamburg CLN2 disease scale will be compared with historical natural history data from the registry at the University Medical Center in Hamburg, Germany and/or data from siblings with CLN2 disease, as appropriate.

9.3 Selection of Study Population

Pediatric patients (from birth to < 18 years of age) with confirmed CLN2 disease progression may be eligible to participate in this study. Additional criteria for participation in this study are detailed below. Subjects must satisfy the following criteria in order to enroll in the study:

9.3.1 Inclusion Criteria

- Diagnosis of CLN2 disease as determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at Screening. *Note: Blood for TPP1 enzyme activity and CLN2 gene analysis must be collected to be analyzed centrally.*

- Quantitative clinical assessment of the Hamburg motor-language aggregate score 3-6 at Screening, as defined in the Ratings Assessment Guideline.
- < 18 years of age at the time of informed consent
- Written informed consent from parent or legal guardian and assent from subject, if appropriate
- Males and females who are of reproductive age should practice true abstinence, defined as no sexual activity, during the study and for 6 months after the study has been completed (or withdrawal from the study). If sexually active and not practicing true abstinence, males and females of reproductive age must use a highly effective method of contraception while participating in the study.
- Ability to comply with protocol required assessments (ICV implantation, drug administration, laboratory sample collection, EEG, ECG, MRI, etc.)

9.3.2 Exclusion Criteria

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

- Another inherited neurologic disease, e.g., other forms of CLN or seizures unrelated to CLN2 disease (patients with febrile seizures may be eligible)
- Another neurological illness that may have caused cognitive decline (e.g., trauma, meningitis, hemorrhage) or interfere with disease rating (autism) before Screening
- Percutaneous feeding tube placement prior to enrollment
- Has received stem cell, gene therapy, or ERT
- Contraindications for neurosurgery (e.g., congenital heart disease, severe respiratory impairment, or clotting abnormalities)
- Contraindications for MRI scans (e.g., cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain)
- Episode of generalized motor status epilepticus within 4 weeks before the First Dose visit
- Severe infection (e.g., pneumonia, pyelonephritis, or meningitis) within 4 weeks before the First Dose visit (enrollment may be postponed)
- Presence of ventricular abnormality (hydrocephalus, malformation)
- Presence of ventricular shunt
- Has known hypersensitivity to any of the components of BMN 190

- Has received any investigational medication within 30 days before the first infusion of study drug or is scheduled to receive any investigational drug other than BMN 190 during the course of the study
- Has a medical condition or extenuating circumstance that, in the opinion of the investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability
- Pregnancy any time during the study; a female subject judged by the investigator to be of childbearing potential will be tested for pregnancy

9.3.3 Removal of Subjects from Treatment or Assessment

Subjects (or their legally authorized representatives) may withdraw consent for study participation any time without prejudice; investigators must withdraw from the study any such subject. At the discretion of investigator clinical judgment, a subject may be withdrawn from the study any time. When possible, an Early Termination visit should be scheduled (Section 12.10).

It is a priority of the study to maximize study subject retention and adherence to study-specific procedures. Since study data completeness may affect integrity and accuracy of study results, any subject who suspends or discontinues study treatment should be encouraged to continue study-specific procedures for the remainder of the study. Subjects may suspend or discontinue study medication but should be encouraged to be evaluated per study-specific visit schedule and to undergo all required study procedures and assessments.

The investigator (or designee) must contact the BioMarin medical monitor when a subject discontinues from the study. BioMarin reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual investigator or study site for poor enrollment or noncompliance with the protocol or regulatory requirements.

Reasons for which the investigator or BioMarin may withdraw a subject from the study include, but are not limited to, the following:

- Subject experiences a serious or intolerable AE
- Subject develops a clinically significant laboratory abnormality
- Subject requires medication or medical procedure prohibited by the protocol
- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or does not meet entry criteria

- Subject is lost to follow-up

If a subject fails to return for a scheduled visit, 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 that s/he contact the investigator. A copy of this letter and any response should be kept in the study records. If the subject cannot be contacted or fails to respond, the subject will be considered lost to follow-up.

The investigator (or designee) must explain to each subject before enrollment in the study that the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB/IEC/REC. It is the responsibility of the investigator (or designee) to obtain written permission to use protected health information per country-specific regulations, such as HIPAA in the US, from each subject or (legally authorized representative, if appropriate). 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.

9.3.3.1 Stopping Criteria

As described in Section 10.2.3.2, all AEs, including toxicity of study drug, will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse AEs (CTCAE) v. 4.0

Hypersensitivity reactions, including anaphylaxis and less severe allergic reactions, are identified risks of ERT. For hypersensitivity or allergic-type reactions, unacceptable drug-related toxicity shall be defined as a NCI CTCAE v. 4.0 Grade 3 or higher AE that is study-drug related in the opinion of the investigator and meets either of the following criteria:

- Shows no improvement with medical intervention, such as infusion interruption, infusion rate reduction, or administration of intravenous antihistamine, oxygen, intravenous fluids, or steroids; or
- Recurs during subsequent infusions at the same or worse severity and intensity, despite any of the following: premedication with appropriate antihistamines, antipyretics, or steroids; and modification of infusion rate.

Instances of unacceptable drug-related toxicity should be discussed by the investigator with the BioMarin medical monitor. A subject who experiences unacceptable drug-related toxicity may be withdrawn from study treatment after consultation with the BioMarin medical monitor.

The normal infusion will be administered over 4 (±1) hours at a rate of 2.5 mL/hr; the dose will be determined by the patient's age. Subjects not receiving the full 300 mg dose (administered in a total volume of 10 mL) will receive the appropriate volume at a rate of 2.5 mL/hr for over a shorter duration of time (See Section 9.4.1). Dosing can be adjusted in the judgement of the investigator, upon consultation with the medical monitor, to manage AEs as outlined in Table 9.4.1.1.

For all events not hypersensitivity or allergic-type reactions, the following will apply:

- If a subject has a Grade 3 or higher AE based on NCI CTCAE v. 4.0 that, in the investigator's opinion, is not related to the subject's underlying disease, consideration will be given to discontinuing the subject from treatment depending on the nature of the event and its persistence. This decision will be made by the investigator in consultation with the BioMarin medical monitor, who may consult the Data Review Board (DRB).
- If two subjects experience the same NCI CTCAE v. 4.0 Grade 3 AE, or if one subject has a Grade 4 AE that, in the investigator's opinion, is not related to the underlying disease, the BioMarin medical monitor will consult the DRB to evaluate the risk/benefit of continuing the study.

Another possible AE is infection from or failure of the indwelling ICV catheter. If an infection is suspected, blood and CSF samples will be drawn for assessment. The subsequent course of therapy, which is guided by site neurosurgical standards of care, may include antibiotic therapy, catheter reposition, or catheter withdrawal. If BMN 190 treatment is suspended, BMN 190 may resume if no more than 4 consecutive missed doses elapse after the last given dose.

If BMN 190 treatment is suspended for any reason, study participation may resume if no more than 4 consecutive doses were missed from the prior given dose.

If two or more subjects experience unacceptable drug-related toxicity, BioMarin may suspend further enrollment in the study pending a review of the data and upon consultation with the DRB. Depending on the nature and severity of the unacceptable drug-related toxicity, dosing of subjects already enrolled in the study may be continued or suspended pending further review. BioMarin will consult the DRB to aid in evaluating the risks of continuing the study and options for modification of the study to minimize subject risk.

Subjects who have a loss of 3 or more points on the combined motor and language components of the Hamburg CLN2 rating scale in any 1 year period may be discontinued at the discretion of the Investigator.

Subjects with a score of 0 on the combined motor and language components of the Hamburg CLN2 rating scale at two consecutive visits will be discontinued from treatment.

9.3.4 Subject Identification and Replacement

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

Subjects who discontinue the study will not be replaced.

9.3.5 Duration of Subject Participation

Subject participation will involve surgical implantation of the ICV access device followed by 14 to 28 days of post-operative recovery and will continue for at least 144 weeks of treatment for all subjects. Treatment will continue until all procedures are completed, the subject withdraws consent and discontinues from the study, is discontinued from the study by the investigator, or the study is terminated by BioMarin. A Safety Follow-Up visit will be conducted 6 months after the final BMN 190 infusion, but will not be required if the subject enrolls in an extension study, registry, or otherwise has continued access to BMN 190 within 6 months after the last infusion (refer to Section 10.2.1 for AE/SAE reporting instructions).

BioMarin reserves the right to discontinue the study any time for clinical or administrative reasons and to discontinue participation of an individual investigator or site for clinical or administrative reasons, including, but not limited to, poor enrollment or noncompliance with procedures of the protocol or GCP.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin or its designee will be responsible for shipping study drug to clinical sites.

9.4.1 Treatments Administered

BMN 190 will be administered by ICV infusion every 14 days ($\pm$3 days), preferably in the morning, according to the patient's age:

- birth to < 6 months: 100 mg
- 6 months to < 1 year: 150 mg
- 1 year to < 2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- $\geq$2 years: 300 mg

Patients younger than 2 years will start the study at the dose level appropriate for their age and will transition to the dose level consistent with their age as they mature.

Fasting for a minimum of 2 hours may be considered for the first infusion and subsequent infusions until the subject's reaction to the study drug is determined. When a feeding tube is used, the tube may be turned off 2 hours before infusion.

The normal infusion will be administered over 4 (±1) hours at a rate of 2.5 mL/hr; the dose will be determined by the patient's age. Subjects not receiving the full 300 mg dose (administered in a total volume of 10 mL), will receive the appropriate volume at a rate of 2.5 mL/hr for over a shorter duration of time (see Table 9.4.1.1 below).

Table 9.4.1.1: Age-Specific Dosing Schema for BMN 190 Administration

Age	Dose	Rate	Infusion Time	Dose Modification Options (AEs)
birth to < 6 months	100 mg	2.5 mL/hr	1.3 hours (±0.5 hr)	• Reduce infusion rate and administer drug over 2 hours • Reduce the dose by 50% administered over the 1.3 (± 0.5) hours • Reduce the infusion rate and administer 50% of the target dose over 2 hours
6 months to < 1 year	150 mg	2.5 mL/hr	2 hours (±0.5 hr)	• Reduce infusion rate and administer drug over 3 hours • Reduce the dose by 50% administered over the 2 (± 0.5) hours • Reduce the infusion rate and administer 50% of the target dose over 3 hours
1 year to < 2 years	200 mg (first 4 doses), 300 mg (subsequent doses)	2.5 mL/hr 2.5 mL/hr	2.7 hours (±1 hr) 4 hours (±1 hr)	• Reduce infusion rate and administer drug over 4 hours (200 mg); 6 hours (300 mg) • Reduce the dose by 50% administered over the 2.7 (± 1) hours (200 mg); 4 (± 1) hours (300 mg) • Reduce the infusion rate and administer 50% of the target dose over 4 hours (200 mg); 6 hours (300 mg)
≥2 years	300 mg	2.5 mL/hr	4 hours (±1 hr)	• Reduce infusion rate and administer drug over 6 hours • Reduce the dose by 50% administered over the standard time of 4 (± 1) hours • Reduce the infusion rate and administer 50% of the target dose over 6 hours

Dosing can be adjusted in the judgement of the investigator, upon consultation with the medical monitor, to manage AEs as outlined above. Should the dose-limiting AE resolve in

the opinion of the investigator, and upon consultation with the medical monitor, dosing at the full dose may resume.

In patients younger than 2 years, dosing may also be adjusted by the sponsor in consultation with the investigator and medical monitor based on results from PK analysis, as follows:

- Within a patient, if the observed CSF AUC_{0-t} exceed the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be reduced to 50% of the recommended age-appropriate dose.
- Within a patient, if the observed CSF AUC_{0-t} is less than the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be increased to the recommended dose for the next oldest age group.

9.4.2 Identity of Investigational Product

9.4.2.1 Product Characteristics and Labeling

The study drug label includes, but is not limited to, the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address.

9.4.3 Storage

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

9.4.4 Directions for Administration

Surgical implantation of an ICV reservoir will take place prior to study drug administration. The investigator will evaluate the patency, location, and skin integrity of the reservoir at each study drug administration (refer to the Study Pharmacy Manual). At each administration, the investigator will draw 1-2 ml of CSF into the device cannula to check for patency prior to administering the study drug. This volume of CSF is also to be used for laboratory testing (cell count, protein, glucose, and culture) as noted in Table 9.1.1. Access to the device is performed using strict sterile technique. Skin covering the reservoir is inspected for an appropriate needle insertion site. The needle insertion site must be intact, without evidence of breakdown, wound, infection or rash. The needle used is a small gauge non-boring tip. Once the reservoir has been accessed, the needle is immobilized to ensure minimal movement or risk of removal. If the needle dislodges during an infusion, it may not be reinserted, as sterility has been compromised. At the discretion of the investigator and/or neurosurgeon, the

reservoir may be replaced during the clinical study. Refer to Section 7.4.2 for risks associated with the implantation procedure.

All study subjects will be administered BMN 190 by ICV infusion every 14 days (±3 days), preferably in the morning. Fasting for a minimum of 2 hours may be considered for the first infusion and subsequent infusions until the subject's reaction to the study drug is determined. When a feeding tube is used, the tube may be turned off 2 hours before infusion. Study procedures for each study visit should precede study drug infusion unless otherwise specified. The date, time, volume, and concentration of each dose of study drug administered to each subject will be recorded in the dispensing log provided for the study as well as on the appropriate eCRF. The Study Pharmacy Manual provides further instructions on preparation and administration of study drug.

Subjects will be admitted to the hospital for every BMN 190 infusion. For all infusions, subjects will be monitored in an appropriate inpatient setting for a minimum of 24 hours from the start of the infusion. For the first infusion only, subjects will also return for a follow-up visit to clinic 72 hours (and no later than the third calendar day) after the start of infusion. After all visits, the parent or legal guardian will be telephoned within 48 hours to determine health status.

Because hypersensitivity reactions may be associated with ERT administration, subjects should be pretreated with age-appropriate doses of antihistamine (and antipyretic, if appropriate) medication approximately 30 minutes (± 15 minutes) before BMN 190 infusions. Subjects may be pretreated, at the discretion of the Investigator, with age-appropriate sedative medication approximately 30 minutes (± 15 minutes) before BMN 190 infusion according to institution’s standard practices. Clinical, developmental, and QOL assessments are to be performed before premedication for infusions.

The normal infusion will be administered over 4 (±1) hours at a rate of 2.5 mL/hr; the dose will be determined by the patient’s age. Subjects not receiving the full 300 mg dose (administered in a total volume of 10 mL) will receive the appropriate volume at a rate of 2.5 mL/hr for over a shorter duration of time (see age-specific dosing table in Section 9.4.1). Uniform infusion rate should be ensured by use of a syringe pump with appropriate delivery range, delivery rate accuracy, and alarms for incorrect delivery or occlusion. If the dose needs to be stopped for safety or other reasons, it may be restarted at the same rate and completed so long as the total dose is administered within 10 hours of preparation of the dose syringes.

Dosing can be adjusted in the judgement of the investigator, upon consultation with the medical monitor, to manage AEs as outlined in Table 9.4.1.1. Should the dose-limiting AE

resolve in the opinion of the investigator, and upon consultation with the medical monitor, dosing at the full dose may resume.

In patients younger than 2 years, dosing may also be adjusted by the sponsor in consultation with the investigator and medical monitor based on results from PK analysis, as follows:

- Within a patient, if the observed CSF AUC_{0-t} exceed the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be reduced to 50% of the recommended age-appropriate dose.
- Within a patient, if the observed CSF AUC_{0-t} is less than the range of CSF AUC_{0-t} characterized with the 300 mg dose in Study 190-201, the dose may be increased to the recommended dose for the next oldest age group.

9.4.4.1 Safety Monitoring

Following ICV access device placement, subjects and their caregivers will be given written instructions providing details on signs and symptoms of concern for device complications and instruction on when to return to the site for device evaluation. Patients will be admitted to the hospital for every BMN 190 infusion. For all infusions, subjects will be monitored in an appropriate inpatient setting for a minimum of 24 hours from the start of the infusion. For the first infusion only, subjects will also return for a follow-up visit to clinic 72 hours (and no later than the third calendar day) after the start of infusion. After all visits, the parent or legal guardian will be telephoned within 48 hours to determine health status.

Vital signs (Section 9.7.5.1) will be measured within 30 (±5) minutes before infusion start or restart, every 30 (±5) minutes during infusion, 0.5 hours (±5 minutes), 1 hour (±5 minutes), and 4 hours (±15 minutes) after infusion end, and then every 4 hours (±15 minutes) for the next 16 hours. Blood pressure will be measured in the upper arm using an appropriately sized blood pressure cuff. If the patient's blood pressure is abnormal (as compared to site-specific reference ranges), a manual blood pressure will be obtained by a trained healthcare professional.

For the first infusion of BMN 190, continuous ECG monitoring (3- or 5-lead) will be performed for all subjects. The ECG should begin 15 (± 5 minutes) prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. In the event that the subject has already received the first infusion of BMN 190, the next infusion will be monitored as above. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG.

A standard ECG (12-lead), including heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities, will be performed 30 (±5) minutes after infusion end at the first infusion and every 24 weeks thereafter. In patients with present or past bradycardia,

conduction disorders, or with structural heart disease, an ECG will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, 30 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end for each study drug infusion.

Subjects require regular monitoring for adverse events and epileptic seizures by appropriately trained personnel throughout the duration of the infusion. If epileptic seizures develop, the infusion may be interrupted at the discretion of the investigator. Because hypersensitivity reactions (anaphylaxis or general allergic) may occur, it is required that appropriately trained personnel and equipment for emergency resuscitation (including epinephrine) be available near the bedside during study drug infusion. In case emergency treatment is needed, all subjects should have an intravenous line during infusion. If the prior 3 study drug infusions were completed without significant adverse events, an intravenous access line does not have to be placed prior to infusion as consistent with local hospital policies. However, supplies for placing emergency access and all emergency medication must be readily available should they be needed. For information regarding the reporting of hypersensitivity reactions, refer to Section 10.4.1.

Symptoms of hypersensitivity reactions may include fever, chills/rigors, skin symptoms (urticaria, angioedema, rash), respiratory symptoms (dyspnea, wheezing, stridor), gastrointestinal symptoms (nausea, vomiting, abdominal pain), and/or cardiovascular changes (hypotension/hypertension). If more severe symptoms, such as angioedema (tongue or throat swelling) or stridor, develop, the infusion should be stopped.

To date there has been no anaphylaxis or anaphylactoid reactions in studies with BMN 190. However, in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or severe hypersensitivity (defined as a hypersensitivity event of Grade 3 or higher), blood samples to assess C4, serum tryptase, and total IgE will be collected within 1 hour of the event and tested; a blood sample to assess drug-specific IgE will be collected no sooner than 8 hours after the event (or before the next infusion).

Safety assessments will be conducted during and after each infusion. Subjects may be required to stay for a longer observation period at the investigator's discretion. If an AE consistent with a hypersensitivity reaction (Section 7.4.1) is observed, appropriate intervention may include infusion interruption, infusion rate decrease, or administration of antihistamine, oxygen, fluids, or steroids. If infusion is restarted after interruption, the initial rate should be approximately one-half the rate at which the reaction occurred. Further detail for infusion modification is provided in the Study Pharmacy Manual.

The parent or legal guardian will be instructed to contact the investigator to discuss any AE subsequent to discharge.

The use of ICV access devices can result in infections, intracerebral hemorrhage from chronic reservoir use, reservoir leakage, and seizures (Karavelis, 1996) (Kronenberg, 1998). Additional surgery may be required to fix or replace the devices. Patients will be monitored throughout the study for potential infections (high temperature, cough, rash, headache, swelling or drainage in the incision area) and signs of ICV reservoir leakage or failure (refer to the Study Pharmacy Manual).

Because of the inherent safety considerations surrounding the implanted device, arrangements should be made for the subject to have the ICV access device removed no more than 4 weeks after either the Study Completion visit or the Early Termination visit.
All removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and all other devices (as described in the Pharmacy Manual) except for infusion pumps, should also be returned. If the subject intends to continue to receive BMN 190 following participation in this study (e.g., via commercial product, use in a registry, or another BMN 190 study), then the device does not need to be removed. Following device removal, subjects should return to the site 4 weeks (±3 days) later for a safety follow-up visit.

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be enrolled as they become available and without attention to any entry criterion or other patient characteristic.

9.4.6 Selection of Dose

BMN 190 will be administered by ICV infusion every 14 days (±3 days) according to the patient's age:

- birth to < 6 months: 100 mg
- 6 months to < 1 year: 150 mg
- 1 year to < 2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- ≥2 years: 300 mg

Patients younger than 2 years will start the study at the dose level appropriate for their age and will transition to the dose level consistent with their age as they mature.

The 300 mg dose level was derived from dose levels used in the TPP1-null dachshund study (Vuillemenot, 2011). Pharmacological effects, including functional improvement and life extension, have been robustly demonstrated in TPP1-null dachshunds at 4 mg and

16 mg dose levels. Since TPP1 activity in brain tissue is proximally related to CNS lysosomal storage materials, scaling by brain mass is judged to be predictive of the human therapeutic dose. Human-equivalent doses were calculated by brain mass scaling. The human brain on average achieves about 75% of adult mass by age 2 and 100% by age 5 (Giedd, 1996). If adult human brain mass is 1400 g, the range for healthy children aged 2 to 7 years would be 1050 to 1400 g. Given progressive brain atrophy in CLN2 disease patients, an average mass of 1000 g was assumed, producing a scaling factor of 20-fold based on average dachshund brain mass of 50 g.

The no-observed-adverse-effect level (NOAEL) which also yielded clinical disease benefit from nonclinical studies in Dachshund was 48 mg, which would correspond to 960 mg in human.

BMN 190 dose scaling by brain mass has been used to target similar drug concentrations in CNS tissue and scaled doses have yielded similar PK in CSF when applied across species (i.e., dog, monkey and human). This approach supports a dose of 300 mg every 14 days down to 1 year of age, where the human brain has reached approximately 68-73% of its adult mass, or 0.94 kg and 0.97 kg for females and males, respectively (Dekaban, 1978). Subjects less than 1 year of age will receive a reduced dose, scaled by brain mass, and will escalate to the next dose level as they age on the study. As an additional precaution, subjects aged between 1 to < 2 years will receive an initial dose of 200 mg for the first 4 doses to assess the safety, tolerability and PK of BMN 190 before being escalated to the 300 mg dose level. This dosing plan enables enrollment of subjects who are younger than 2 years of age.

The age-specific dose of BMN 190 will be infused at a uniform rate of 2.5 mL/hour for all subjects, thus requiring shorter total infusion times for subjects administered doses lower than 300 mg. The total infusion volume and infusion rate is within the physiologic functional range in relation to the brain volume, CSF volume and CSF turnover rate of children < 3 years of age. The total volume of CSF in an infant is approximately 50 mL, thus the total volume of BMN 190 infused (3.3 mL) is less than 10% of this volume. Furthermore, since at least 2 mL of CSF will be collected prior to each infusion for surveillance laboratory testing, the total drug volume infused is not expected to be of physiologic consequence as it pertains to changes in intracerebral pressure.

CSF production rates in humans have been calculated to be 0.3–0.4 ml/min, which translates to an hourly production rate of approximately 20 ml (Pappenheimer, 1962). A more recent retrospective study of 100 children (61 males, 39 females; age 0.02 to 15.7 years) with hydrocephalus due to various causes measured hourly CSF production output as reflected by the output through an external ventricular drainage (EVD) (Yasuda, 2002). The mean (SD)

hourly rate of CSF output was 8.1 (5.2) mL/h. A regression analysis indicated that the age and body weight appeared to correlate with the hourly CSF output. The regression equation is as follows: hourly CSF output = 2.78 – 2.23(male = 0, female = 1) + 0.97 log (age in years) + 2.26 log (body weight in kg). Thus, the predicted hourly CSF output even for a 6 month old child be approximately 2.5 to 4.7 mL, which exceeds the hourly rate of BMN-190 infusion of 2.5 mL, suggesting that the infusion rate is compatible with CSF physiology.

Lastly, this dosing strategy also has the added benefits of shortening the total infusion time for infants (approximately 1.3 to 1.5 hours) and toddlers (approximately 2.7 hours) and decreasing the possibility of dosing errors (since the smaller volume will be administered at a consistent rate).

The PK of BMN 190 will be assessed in this study to further confirm the appropriateness of this approach. In children younger than 2 years, dosing may be adjusted based on PK as described in Section 9.4.1.

9.4.6.1 Selection of Timing of Dose for Each Subject

A mean CNS half-life of approximately 2 weeks (PI) suggests biweekly dosing may sustain therapeutic BMN 190 levels in the CNS. BMN 190 concentrations in CSF remained above the lysosomal K_{uptake} for approximately 48 hours after single ICV or IT-L infusions in species with CSF dynamics similar to those in human (Vuillemenot, 2014), (Vuillemenot, 2011); PI). In these same species (dog and monkey), CNS distribution of BMN 190 was extensive in many brain regions.

9.4.6.2 Selection of Infusion Volume and Rate

The nonclinical studies in the dachshund and cynomolgus monkey utilized an infusion rate of approximately 5% of the total CSF volume per hour. This was expected to represent a safe infusion rate that would minimize changes in total CSF volume and intracranial pressure. The dachshunds received ICV infusions at a rate of 0.6 mL/hour for 2-4 hours, while monkeys received 0.88 mL/hour for 3.6 hours. No effects were observed in these studies indicative of safety concerns due to the infusion rate. In the CLN2 patient population, the estimated CSF volume is approximately 100 mL. For the proposed clinical trial, a volume of 10 mL infused over a 4 hour period represents an infusion rate of 2.5% of the total CSF volume per hour, which is approximately half the rate that had no safety effects in the nonclinical studies.

Therefore, we expect that 10 mL infused over 4 hours would be safe in CLN2 patients. This infusion rate has been used, with acceptable results, in the 48-week, Phase 1 / 2, 190-201 clinical trial (completed) and ongoing 190-202 extension study.

In subjects less than 2 years of age, the infusion volume will be reduced in accordance with their age-specific dose (Section 9.4.1) to account for differences in brain mass and CSF volume in younger subjects.

9.4.7 Blinding

This is a single-arm, open-label study. Study site assessments of safety and clinical severity will be performed without blinding to treatment and subjects will be enrolled as they become eligible.

As defined in the Imaging Charter, oversight of MRI evaluation will be performed by independent radiologists at a central imaging facility. The interpreting radiologists and software analysis will be blinded to subject and time on study. All subject-identifying information will be redacted before endpoints are assessed.

Oversight of EEG evaluation will be performed by an independent epileptologist at a central facility. The interpreting epileptologists and software analysis will be blinded to subject and time on study. All subject-identifying information will be redacted before endpoints are assessed.

9.4.8 Prior and Concomitant Medications

Medications (prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days before informed consent will be recorded in the eCRF at Screening. At each subsequent visit (or within one week of the Early Termination visit), change in any medication (dosage, frequency, new medication, or cessation) since the previous visit will be recorded in the eCRF.

Any concomitant medication added or discontinued during the study should be recorded in the eCRF (or within 1 week of the Early Termination visit).

Subjects may be taking anticonvulsants and medications for myoclonus, tremor, agitation, and pain. Investigators will be asked to keep these regimens constant throughout the study, unless changes are required due to lack of efficacy or toxicity.

Use of non-drug therapies such as physical and occupational therapy will also be noted in the eCRF.

9.4.9 Treatment Compliance

Study drug will be administered to subjects at the study site by a qualified professional. Date, time, volume, and concentration of each dose must be recorded in the dispensing log as well as on the appropriate eCRF. In the event that a dose of study treatment is missed or incomplete, the investigator should record the reason and any other pertinent information on the eCRF as appropriate.

9.5 Investigational Product Accountability

The investigator or designee is responsible for maintaining accurate records (including dates and quantities) of study drug received by each subject and study drug 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 accountability data.

9.5.1 Return and Disposition of Clinical Supplies

Unused study drug 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 study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to BioMarin and retained in investigator study files. If a study site is unable to destroy study drug appropriately, the site may return unused study drug to a BioMarin-designated facility for destruction. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by BioMarin.

All study drug 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

There are no dietary or other protocol restrictions for this study. Subjects who require a PEG (percutaneous endoscopic gastrostomy) tube as the standard of care during the course of the study will be allowed to continue in the study. When a feeding tube is used, the tube may be turned off 2 hours before infusion.

9.7 Efficacy and Safety Variables

Efficacy will be measured using the 0 to 6-point ML score on the Hamburg CLN2 rating scale as the primary endpoint. The 12-point total score (motor, language, vision, and seizure

subscales) on the Hamburg CLN2 scale, time to disease manifestation (for asymptomatic patients), and MRI measures of disease progression will be collected as secondary endpoints.

Exploratory efficacy measures will include developmental status, involuntary movements, retinal anatomy using OCT, seizure frequency, change in seizure activity (as measured by Hamburg score), anti-epileptic treatment, quality of life metrics, changes in EEG, assessment of visual acuity, and analysis of disease-related biomarkers.

Timing of study assessments is detailed in the Schedule of Events (Table 9.1.1).

9.7.1 Efficacy Variables

9.7.1.1 CLN2 Clinical Rating Scale

Disease severity will be evaluated by the CLN2 clinical rating scale (Steinfeld, 2002); (Worgall, 2008). This scale consists of 4 domains with intrinsic content validity. Within each domain, a score from 0 to 3 is assigned and overall scores are calculated by summing the four domain scores for a final rating of 0 (severely impaired) to 12 (normal).

Since the motor and language domains are most relevant to CLN2 disease progression (Section 9.2), they will be used to assess study eligibility and efficacy (Appendix 1). To be eligible for study participation, motor/gait and language domains administered during Screening must document confirmed CLN2 disease progression by a total score of 3-6 for these 2 domains, as defined in the Ratings Assessment Guideline.

Raters will be identified as qualified practitioners, who have been trained on the definitions and implementation of the CLN2 disease rating scale. All raters at all sites will be required to pass a training session designed to standardize the definitions and scale anchor points across the study, before study ratings take place. Whenever possible, a single rater should evaluate each enrolled patient for the duration of treatment. Further, patient ratings should take place at the same time in the study visit, preferably in the morning before procedures and/or infusion takes place. CLN2 scale assessments should be done prior to pretreatments for BMN 190 infusion.

9.7.1.1.1 Videotaping

Rating scale assessments will be videotaped in a standardized manner across all study sites. The Ratings Assessment Guidelines provide detailed instructions for videotaping. All CLN2 disease scale evaluations will be videotaped. Videotapes are used to corroborate clinical assessments and there are no efficacy outcomes associated with analysis of videotapes.

9.7.1.2 Magnetic Resonance Imaging

All image data will be acquired on a 1.5 Tesla MRI platform. Study MRIs will include localizer, 3D T1-weighted sagittal, T2-weighted gradient-echo, diffusion-weighted axial and FLAIR axial acquisitions, as specified in the Imaging Charter. Total scanner time is less than 60 minutes and is expected to be accomplished in the majority of subjects with sedation. Volumetric analysis of images will be done by estimating both volume of total cortical grey matter and proportion of the cranial CSF.

All patients will have an MRI without contrast prior to implantation of the ICV access device, to ensure proper planning and placement. No study assessments associated with an MRI will be performed at the time of this MRI, and any readings taken during this MRI will not be included in the analysis of study data.

An MRI scan also should be performed whenever infection or shunt dysfunction is suspected by the investigator. In this case, according to the Imaging Charter, the MRI should be with or without intravenous contrast with at least T1-weighted axial and sagittal aspects. For suspected meningitis, an MRI of the brain should be performed with and without contrast, according to the Imaging Manual.

9.7.1.3 Denver Development Scale II

The Denver II is a revision and update of the Denver Developmental Screening Test. Both tests were designed to monitor the development of infants and preschool-aged children. The tests cover four general functions: personal social (such as smiling), fine motor adaptive (such as grasping and drawing), language (such as combining words), and gross motor (such as walking). Ages covered by the tests range from birth to 6 years.

9.7.1.3.1 Modified Unified Batten Disease Rating Scale Involuntary Movement Inventory

The modified Unified Batten Disease Rating Scale (mUBDRS) Involuntary Movement inventory is a rating scale that measures the type, frequency and severity of common involuntary movements associated with CLN2 disease such as myoclonus and dystonia.

9.7.1.4 Optical Coherence Tomography

Optical coherence tomography (OCT) is a non-invasive imaging test that uses light waves to take cross-sectional pictures of the retina's layers in order to measure their thickness. These measurements can aid in early detection and treatment for retinal diseases. OCT will be performed locally and should precede infusions. In order to limit the need for sedation to

perform this assessment, measurement should be obtained while the subject is also under sedation for MRI acquisition.

OCT images will be collected by BioMarin, to be assessed by BioMarin personnel or designees.

9.7.1.5 Modified Unified Batten Disease Rating Scale Seizure Inventory

The mUBDRS Seizure Inventory measures the type and frequency of seizures in CLN2 patients in the prior 3 month interval. The inventory is completed with the aid of caregiver/family member recall in the period between study visits.

9.7.1.6 PedsQL

The PedsQL™ Generic Core Scales are designed to measure Quality of Life in children and adolescents. The assessments are brief, practical and developmentally appropriate.
The instrument is responsive to clinical change over time (Msall, 2005). The four parent reports cover the ages from 1-12 months, 13-24 months, 2-4 years, and ≥ 5 years, and include questions regarding physical, emotional, and social functioning, with school functioning where applicable. Patients who become older than age 5 during the study will no longer be assessed using this tool.

9.7.1.7 CLN2-specific QoL Questionnaire

The CLN2-specific QoL Questionnaire is a disease specific supplement to the PedsQL using the same format and quantitation. The questionnaire is a novel instrument that was designed in collaboration with patient family and advocacy groups to capture elemental care and quality of life issues in late infantile CLN2 disease.

9.7.1.8 Electroencephalogram

A standard awake EEG will be recorded within 2 days before each infusion. If a clinically significant abnormality is noted, the investigator or designee will evaluate whether study enrollment or continuation is appropriate; a clinically significant abnormality will be recorded under Medical History during Screening.

9.7.1.9 Assessments of Visual Acuity

The Preferential Looking Test (PLT) is a method of assessing visual acuity in infants and children with limited cognitive function. The PLT assesses the acuity of children who are unable to identify pictures, shapes, or letters, and is particularly useful in children with physical and/or mental disabilities. The principle of the test is that a young child will choose to look towards an interesting visual stimulus (“target”) rather than a plain stimulus.
The child is presented with two stimulus fields, one with stripes and the other with a

homogeneous gray area of the same average luminance as the striped field. The location of the stripes is randomly alternated. Typically, infants and children will look at the more interesting stripes (if they can detect them) rather than at the blank field. Teller, Keeler, and LEA Grating Acuity Cards have been standardized to assess grating (resolution) visual acuity in infants and nonverbal children using the principles of Preferential Looking.

Other standardized versions of the LEA Test System use symbols or numbers to assess visual acuity in children who do not know how to read the letters of the alphabet that are typically used in an eye chart, but require higher cognitive function than PLT. The symbols are likely to be more useful in the CLN2 patient population. Similarly, the E-Hook or Tumbling E chart has been standardized to use rows of the letter "E" in various orientations. The patient is asked to point to where the limbs of the E are pointing "up, down, left or right." Depending on how far down the chart the patient can "read", his or her visual acuity is quantified.

All subjects will perform PLT. Use of standardized Teller, Keeler, or LEA Grating Cards to perform PLT are all acceptable based on institutional standards and availability of personnel experienced in performing the assessments. The choice of testing materials should be consistent for all patients at each investigational site. In addition, for those children who retain the cognitive function to adhere to testing, the Lea Vision Test or Tumbling E Vision Test should also be performed during the same assessment using standardized techniques. The choice of additional assessments for higher functioning children (eg, LEA symbol or Tumbling E) should be made based on availability of experienced and qualified personnel to perform the assessment and should remain consistent throughout the study. Whenever possible, all tests of visual acuity should be performed by the same tester.

The tests of visual acuity may be done either before or after drug infusion based on logistical considerations and ease for the subject and study personnel. However, the timing should remain consistent for all subsequent assessments. Patients must be alert and not influenced by any sedating medications.

9.7.1.10 Biomarkers

Blood and CSF samples will be collected from subjects at the time points indicated in Table 9.1.1 and may be used to evaluate biochemical, molecular, cellular, and genetic aspects relevant to CLN2 disease, and to develop the assays used for these evaluations. Collection should precede study drug infusion.

Exploratory genetic research to study or try to discover genes that are not yet known to be associated with CLN2 disease is optional.

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

9.7.2 Immunogenicity

Immunogenicity tests will be performed at a specialty laboratory using validated immunogenicity assays on serum and CSF samples. Samples of blood (serum) and CSF will be collected for TAb and NAb testing before the first infusion (Baseline or Week 1 before the infusion), every 12 weeks thereafter, and at the Study Completion Visit. Samples of blood (serum) will be collected for TAb testing at the Device Safety Follow-Up and Safety Follow-Up visits (or within 1 week of the Early Termination visit). Collection must precede infusion. NAb will be tested at baseline and at subsequent time points when TAb is positive.

Baseline samples will be used to obtain a baseline total and drug-specific IgE levels in the event of later hypersensitivity reactions requiring additional lab work.

To date there has been no anaphylaxis or anaphylactoid reactions in studies with BMN 190. However, in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or severe hypersensitivity (defined as a hypersensitivity event of Grade 3 or higher), blood samples to assess C4, serum tryptase, and total IgE will be collected within 1 hour of the event and tested; a blood sample to assess drug-specific IgE will be collected no sooner than 8 hours after the event, or before the next infusion.

9.7.3 Safety Variables

Safety will be determined from incidence, severity, and relationship to BMN 190 of treatment-emergent AEs/SAEs reported during the study. In addition, growth (weight, height), vital signs, physical examination, neurologic examination, ECG, standard clinical laboratory blood (chemistry panel and CBC) and urine tests, standard clinical laboratory CSF tests (cell count with differential, protein, glucose, and culture), and concomitant medications will be monitored.

9.7.3.1 Adverse Events

AEs and SAEs will be recorded as defined in Section 10.1. At each visit, subjects will be asked about new or ongoing AEs since the previous visit.

9.7.3.2 Device Malfunctions

For this study, a medical device is defined as the infusion pump and all contact parts (reservoir and catheter, needles, infusion line with filter, extension sets, and syringes) intended to be used for administration of BMN 190. Device malfunctions should be reported

following the implantation of the ICV reservoir and catheter. A device malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. All removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and all other devices (as described in the Pharmacy Manual) except for infusion pumps, should also be returned. For reporting device-related AEs of special interest, please refer to Section 10.4.1.

9.7.3.3 Clinical Laboratory Assessment

Blood and urine samples will be collected for routine clinical laboratory assessments (blood chemistries, hematology, urinalysis) and analyzed locally. Collection should precede infusion.

Any abnormal test result determined clinically significant by the investigator should be repeated until its cause is determined, the value returns to baseline or within normal limits, or the investigator determines the abnormal value was no longer clinically significant.

All abnormal clinical laboratory pages should be initialed and dated by an investigator, along with a comment regarding clinical significance. Each clinically significant laboratory result is to be recorded as medical history at Screening and as an AE subsequently.

If known, the diagnosis associated with an abnormality in clinical laboratory results considered clinically significant by the investigator should be recorded on the AE CRF.

Table 9.7.3.3.1: Clinical Laboratory Tests

Blood Chemistry	Hematology	Urinalysis
albumin	hemoglobin	appearance
alkaline phosphatase	hematocrit	color
ALT (SGPT)	WBC count	pH
AST (SGOT)	RBC count	specific gravity
direct bilirubin	platelet count	ketones
total bilirubin	differential cell count	protein
blood urea nitrogen		glucose
calcium		bilirubin
carbon dioxide		nitrite
chloride		urobilinogen
total cholesterol		hemoglobin
C-reactive protein		
creatinine		
creatine kinase		
glucose		
GGT		
LDH		
phosphorus		
potassium		
total protein		
sodium		
uric acid		

9.7.3.4 Cerebrospinal Fluid Surveillance

Samples of standard clinical laboratory CSF for routine surveillance (cell count with differential, protein, glucose, and culture) will be collected within 30 (±5) minutes before every infusion. A small volume of CSF will be collected from the ICV reservoir and analyzed locally. Collection should precede study drug infusion.

9.7.3.5 Other Laboratory Assessments

Subjects who experience an SAE possibly related to BMN 190 or other AE of concern may have additional blood samples drawn to assess immunogenicity or safety parameters.

9.7.4 Pharmacokinetics Variables

On Day 1 and Weeks 25, 49, and 97 samples of CSF and plasma for serial PK will be collected within 15 minutes before infusion start, and 0.25, 4, 8, 20 (±5 minutes), 72, and 120 (±15 minutes) hours after infusion completion. The following parameters will be evaluated by non-compartmental analysis:

- Area under concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
- Area under concentration-time curve from 0 to the time of last measurable concentration (AUC_{0-t})
- Maximum observed concentration (C_{max})
- Time to reach C_{max} (T_{max})
- Elimination half-life ($t_{½}$)
- Apparent clearance of drug (CL/F)
- Apparent volume of distribution based on terminal phase (V_z/F)

If a subject discontinues the study within 48 hours after an infusion completion, plasma and CSF samples should be drawn during the Early Termination visit.

9.7.5 Vital Signs, Physical Examinations, and Other Observations

9.7.5.1 Vital Signs

Vital signs (SBP, DBP, heart rate, respiration rate, and temperature) will be measured within 30 (±5) minutes before infusion start (or restart), every 30 (±5) minutes during infusion, 0.5 hours (±5 minutes), 1 hour (±5 minutes), and 4 hours (±15 minutes) after infusion end, and then every 4 hours (±15 minutes) for the next 16 hours. Blood pressure will be measured in the upper arm using an appropriately sized blood pressure cuff. If the patient's blood pressure is abnormal (as compared to site-specific reference ranges), a manual blood pressure will be obtained by a trained healthcare professional.

9.7.5.2 Physical Examination

A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, and musculoskeletal.

A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, and gastrointestinal assessments.

Body weight and height will also be assessed at the timepoints indicated in Table 9.1.1.

Use of an ICV reservoir device for intracerebroventricular drug administration requires that patients be monitored throughout the study for potential infections (high temperature, cough, rash, headache, mental status changes, swelling or drainage in the incision area) and signs of ICV reservoir leakage or failure (swelling of skin around reservoir site, difficulty with CSF extraction, erythema of the scalp, bulging of reservoir device, or extravasation of fluid on infusion).

The investigator will evaluate the patency, location, and skin integrity of the reservoir at each study drug administration. The investigator will check for scalp edema, erythema or skin breakdown at the site of the reservoir prior to infusion. Patency will be assessed during pre-infusion sampling and again at the time of infusion. Difficulty in obtaining the required volume of CSF necessary for pre-infusion samples or signs of ICV reservoir leakage (swelling of skin around reservoir site, erythema of the scalp, bulging of reservoir device, or extravasation of fluid) will prompt further evaluation of the reservoir for failure prior to continuing with infusion. Additional surgical consultation including surgery may be required to fix or replace the device. Material degradation of the ICV device reservoir has occurred after approximately 105 perforations of the ICV device in benchtop testing, and has been observed in clinical trials with approximately 4 years of BMN 190 administration. Access device replacement should be considered prior to 4 years of regular administration of BMN 190; with the decision made on an individual subject level based on the medical judgment of the Investigator. All removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and all other devices (as described in the Pharmacy Manual) except for infusion pumps, should also be returned.

Clinically significant abnormalities will be recorded under Medical History at Screening or as AEs thereafter.

9.7.5.3 Neurological Examination

A complete neurological examination will include level of consciousness, speech, language, cranial nerves, motor strength, motor tone, abnormal movements, reflexes, upper extremity sensation, lower extremity sensations, gait, Romberg, nystagmus, and coordination.

9.7.5.4 Electrocardiogram

For the first infusion of BMN 190, continuous ECG monitoring (3- or 5-lead) will be performed for all subjects. The ECG should begin 15 (± 5 minutes) prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. In the event that the subject has already received the first infusion of BMN 190, the next infusion will be monitored as above. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG.

A standard ECG (12-lead), including heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. ECG will be performed 30 (±5) minutes after infusion end at the first infusion and every 24 weeks thereafter. In patients with present or past bradycardia, conduction disorders, or with structural heart disease, an ECG will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, within 30 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end for each study drug infusion.

If a clinically significant abnormality is noted, the investigator or designee will evaluate whether study enrollment or continuation is appropriate; a clinically significant abnormality will be recorded under Medical History during Screening and as an AE thereafter.

9.7.5.5 Pregnancy Testing

At Screening and at any time during the study, a female subject judged by the investigator to be of childbearing potential (as defined by onset of menses) will be tested for pregnancy with a urine pregnancy test; additional urine tests will be performed whenever pregnancy is in question. A serum pregnancy test will be performed if a urine test result is positive or equivocal.

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 patient administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

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

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

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

10.1.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

  Note: Life-threatening refers to an event that places the patient at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability or incapacity

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

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

10.1.3 Adverse Events of Special Interest (AEoSI)

The following AEoSI need to be reported to the Sponsor within 24 hours of site awareness, irrespective of seriousness, severity or causality, to facilitate real-time monitoring and assessment:

- Status epilepticus
- Hydrocephalus (communicating and non-communicating)
- Meningitis
- Unexpected rapid decline on CLN2 scale not attributable to other causes
- Hypersensitivity
- Temporally-related events
- Device-related events (e.g., infection, prophylactic ICV replacement, malfunction with an associated AE such as leaking reservoir or a problem that ends the administration of study drug for that visit, etc).
    - All removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and all other devices (as described in the protocol Pharmacy Manual) except for infusion pumps, should also be returned.
- Cardiovascular events
- ECG adverse events

10.2 Methods and Timing for Capturing and Assessing Safety Parameters

10.2.1 Adverse Event Reporting Period

The study AE/SAE/AEoSI/pregnancy reporting period is as follows:

- After informed consent and prior to ICV access device implantation: all SAEs related to study-mandated procedures

- After ICV access device implantation but before first dose: all SAEs related to study-mandated procedures and all device-related AEs, except as defined in SAE Exclusion section.
- After first dose: all AEs, SAEs, AEoSI, and pregnancies.

AE/SAE/pregnancy reporting should continue as detailed above until the safety follow-up visit occurs 6 months after the last administration of study drug. The Safety Follow-up visit is not required if a subject enrolls in an extension study or registry or otherwise continues to have access to BMN 190 within 6 months of the final infusion. For subjects who enroll into another BioMarin-sponsored study or registry, AE/SAE reporting is as follows:

- The 190-203 reporting period for new onset AEs/SAEs, pregnancies, and device related events ends when the subject receives the first dose of study drug under the new study or registry.
- Ongoing AEs related to study drug will be followed until resolution under this study.
- All ongoing SAEs, pregnancies, and device-related events will be followed until resolution under this study.

Events that started in this study and worsen after first the dose of study drug in the new study or registry will be captured as a new event under the new study. For subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week Device Safety and 6-month Safety follow-up visit will capture information regarding ongoing events at the time of the last dose or new events related to study drug.

For this study, a medical device is defined as the infusion pump and all contact parts (reservoir and catheter, needles, infusion line with filter, extension sets, and syringes) intended to be used for administration of BMN 190. Adverse events assessed by the investigator as related to the device, including malfunction, injury, or medication error, will be entered into the EDC (electronic data capture). Prophylactic replacement of the ICV must be reported as a device related event. All AEs related to the device will be reported to BPV within 24 hours using the EDC and study specific case report form(s). The reporting period for device-related events begins with reservoir implantation and ends 4 weeks following the final removal of the implanted reservoir and catheter.

10.2.2 Eliciting Adverse Events

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

10.2.3 Assessment of Seriousness, Severity, and Causality

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

10.2.3.1 Seriousness

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

10.2.3.2 Severity

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

The Investigator will determine the severity of each AE and SAE and AEoSI 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 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 CRF. To ensure consistency of causality assessments, Investigators should apply the guidance in Table 10.2.3.3.1.

Table 10.2.3.3.1: Causality Attribution Guidance

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

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate (in compliance with applicable regulations) 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 the eCRF. Avoid colloquialisms and abbreviations.

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

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

10.3.1.1 Diagnosis versus Signs and Symptoms

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

10.3.1.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points with no change in severity. For non-serious AEs, if the severity changes (increases or decreases), a new AE should be entered on the AE eCRF (in which case it should be recorded again on the AE eCRF). AEs characterized as intermittent require documentation of onset and duration of each episode.

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

10.3.1.4 Abnormal Laboratory Values

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

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

A clinical laboratory abnormality should be documented as AE if **any** 1 or more of the following conditions is met:

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

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

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

10.3.1.5 Pre-existing Conditions

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

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

10.3.1.6 Seizure Reporting

Seizures that occur during the subject's enrollment in the study and have not changed in severity, frequency, duration or type from the seizure activity characterized at baseline do not require reporting as an AE/SAE.

AE/SAE Seizure reporting for this study is required for the following situations:

- New onset seizures
- Seizures that have worsened in frequency, severity and/or duration
- Onset new type of seizure

If a subject has more than 1 type of seizure reported at baseline (absence and clonic/tonic), it is important to identify which type of seizure has changed (e.g. more frequent absence seizures, or worsening clonic/tonic seizures). If more than one seizure type is involved, an AE/SAE report form is required for each type that has changed (e.g. worsening drop attacks and new onset clonic/tonic seizure).

Please note for these events, if the seizure returns to baseline seizure activity level then the event would be resolved. If another event of worsening in seizure activity, it would be reported as a new event. If a subject's seizure activity does not return to baseline, but stabilizes so that the new type, frequency or duration is considered the subject's new threshold seizure activity, then the event would considered recovered/resolved with sequelae. Any worsening from this new threshold would then be considered a new event and should be reported as such.

Cluster type seizures do not require reporting of each individualized seizure. Cluster type seizures should be reported using a consistent time frame. For example, if the subject's cluster seizure pattern is 8 to 12 drop attacks a day every 3 days, then this is the baseline time frame for this subject's seizure pattern. If a subject has one clonic/tonic seizure /week, then this is the baseline time frame for this seizure pattern.

Seizures that occur within 24 hours of the start of the BMN 190 infusion should be as an AEoSI and in addition to providing the required assessments, the investigator should indicate if the seizure is consistent with the subject's baseline seizure activity.

10.3.1.7 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition (refer to Section 10.3.1.5). During the study, any new clinically significant findings and/or abnormalities discovered on physical examination that meet the definition of an AE (or an SAE) must be recorded and document as an AE or SAE on the AE eCRF.

10.3.1.8 Hospitalization, Prolonged Hospitalization, or Surgery

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

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

- Perform a protocol-mandated procedure (excluding prophylactic ICV replacement)
- Undergo a diagnostic or elective surgical procedure, which was planned prior to study enrollment, for a pre-existing medical condition.
- Receive scheduled therapy (study drug or otherwise) for the study indication

10.3.1.9 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 (in compliance with applicable regulations) as an SAE.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” or “Death of Unknown Cause” on the eCRF. If the death is attributed to progression of the disease or condition being studied, record “progressive CLN2 disease” as the SAE term on the eCRF.

10.3.1.10 Pregnancy

Although not an AE per se, pregnancy in either a patient or the partner of a patient taking trial medication should be expeditiously reported to BPV in compliance with applicable regulations to facilitate outcome monitoring by the Sponsor. Refer to Section 10.2.1 for pregnancies reporting period.

Pregnancy in a patient or partner should be reported within 24 hours of the site becoming aware of the pregnancy by completing the Pregnancy eCRF and submitting to BPV. In addition, pregnancy in a patient is also reported on the End of Study eCRF. The Investigator must make every effort to follow the patient through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form eCRF. In the event of pregnancy in the partner of a study patient, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

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

10.4 Reporting Requirements

10.4.1 Expedited Reporting Requirements

All SAEs, AEoSI, and pregnancies 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 via eCRF to BioMarin Pharmacovigilance (BPV) within 24 hours of the site becoming aware of the event. If the eCRF system is not available, the SAE must be reported on the study-specific SAE report form and entered into eCRF when possible. If the AE/SAE is assessed as related to the device (or any of its components), in addition to the eCRF entry, the study-specific device report form must be completed and submitted via email/fax within 24 hours of the site becoming aware of the event. Investigators should not wait to collect information that fully documents the event before notifying BPV of an SAE. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit any information requested by BioMarin as soon as it becomes available.

The reporting period for SAEs begins after informed consent is obtained and continues until 6 months following either the last administration of study drug or study discontinuation/termination, whichever is longer (also see Section 10.2.1). The reporting period for device-related events begins with reservoir implantation and ends 4 weeks following removal of the implanted reservoir and catheter.

10.4.2 IRB/IEC Reporting Requirements

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

10.5 Follow-up of Patients after Adverse Events

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

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

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

10.7 Urgent Safety Measures

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

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

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

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

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
Address: 105 Digital Drive
Novato, CA 94949 USA
Phone: PI
E-mail: PI

11 APPROPRIATENESS OF MEASUREMENTS

11.1 Natural History Studies

Two ongoing prospective natural history studies of CLN2 disease (Weill Cornell Medical Center and University Medical Center, Hamburg, Germany) continue to provide evidence that rating scale scores change in a predictable manner with increasing disease duration (Steinfeld, 2002); (Worgall, 2007).

The Weill Cornell database comprises approximately 45 patients with genetically diagnosed CLN2 disease and includes Weill Cornell Scale scores, some Hamburg Scale scores, and MRI data, which have been shared with BioMarin (Crystal, 2004), Approximately half the patients have two assessments 2 weeks to 16 months apart.

The Hamburg registry includes both retrospective and prospective data from approximately 30 patients with CLN2 disease with scoring of 6-month periods from birth to 8-10 years of age. All participants are genetically diagnosed; data include Hamburg Scale scores, neurologic and cardiologic examinations, ophthalmology testing, routine clinical pathology, volumetric MRI, EEG, ECG, and echocardiogram. Although clinical data have accrued for up to 10 years, MRI data collection started in 2009 and these data have been shared with BioMarin (A Schulz and A Kohlschütter, Hamburg).

The Hamburg registry is a subset of Dem-CHILD, a multi-center clinical database of CLN disorders that currently has 72 CLN2 patients. This database continues to add sites and patients, collection of clinical and research information is ongoing.

The natural history data will be used to (1) better understand the properties of the CLN2 disease scale, (2) evaluate correlations between the scale and potential surrogate markers such as neuroimaging, (3) generate the comparison group that will be matched to the study population of this clinical study.

11.2 CLN2 Clinical Rating Scale

Disease severity will be evaluated by the CLN2 clinical rating scale (Steinfeld, 2002); (Worgall, 2008). This consists of 4 domains (Appendix 1), each of which has intrinsic high content validity. Within each domain, a score from 0 to 3 is assigned and overall scores are calculated by summing the 4 domain scores for a final rating of 0 (severely impaired) to 12 (normal).

A clinical rating scale, the Hamburg Scale, was developed to document retrospectively the natural history of CLN2 disease (Steinfeld, 2002). A modified form of that scale, the Modified Hamburg Scale, demonstrated statistically significant slowing of neurologic decline

in subjects receiving gene therapy intervention when compared with decline among control subjects (Worgall, 2008). A second CLN2 disease rating scale, the Weill Cornell Scale (Dyke, 2012); (Worgall, 2007), has also been used to evaluate CLN2 disease severity with highly comparable results.

Although all 4 domains of the Hamburg rating scale will be completed (Appendix 1), the motor and language domains are expected to be most useful for this study. Since these 2 domains are most relevant to CLN2 disease progression, they will be used to assess study eligibility and efficacy. To be eligible for study participation, motor and language domains of the Hamburg CLN2 rating scale administered during Screening must document asymptomatic to moderate CLN2 disease progression with a 2-domain score of 3-6 for these 2 domains, as defined in the Ratings Assessment Guidelines. The planned patient enrollment of at least 10 patients is to include at least 5 patients with a combined ML score $\geq$ 5 points (mild or asymptomatic disease) and at least 5 patients with a ML score < 5 points (moderate disease) to ensure that an equal number of patients with mild and moderate disease are enrolled.

The remaining 2 domains (Appendix 1) are less likely to be informative for this study. Greater detail in the seizure and movement disorders associated with CLN2 disease are captured using a modified UBDRS inventory for involuntary movements and seizures.

Because of practical (limited number of available patients) and ethical (neurosurgery in children with fatal neurologic disease) concerns, this study design cannot involve contemporaneous, matched, randomized, blinded, or untreated control subjects (Arkin, 2005); (Crystal, 2004). Therefore, changes in CLN2 disease scale scores will be compared with historical data from the registry at the University Medical Center in Hamburg, Germany and with data from siblings with CLN2 disease, when available.

11.3 Magnetic Resonance Imaging

As patients progress from mild to severe CLN2 disease, MRI has indicated progressive loss of cortical volume and ventricular enlargement (Worgall, 2007). By late CLN2 disease stages, despite their young age, these patients exhibit substantial atrophy predominantly in the cortical grey matter, comparable to that in elderly people with severe Alzheimer's disease. MRS in patients with CLN2 disease has demonstrated reduced neuronal N-acetyl-aspartate (NAA), reduced NAA/creatine metabolite ratios, and increased myoinositol/creatine ratios when compared with healthy individuals (Seitz, 1998).

Of all 10 MRI measurements examined to quantitate CLN2 disease progression (Worgall, 2007), ventricular volume or percentage ventricular volume correlated most

strongly with age (r^2=0.67-0.87), duration of disease (r^2=0.71-0.79), and severity on clinical rating scales (r^2=0.56-0.76), suggesting that the measurement of ventricular volumes may be the most relevant and sensitive MRI measurement of disease progression. Based on these data, MRI measures of atrophy are more strongly correlated with disease progression than are MRS measures of neuronal viability.

In nonclinical CLN2 disease studies with TPP1-null dachshunds, MRI measurement of ventricular volume enlargement was reduced with BMN 190 treatment. Therefore, this clinical study of CLN2 disease will include MRI measurement of ventricular volume.

12 STUDY PROCEDURES

12.1 Screening

After the nature of the study has been explained, written informed consent by parent or authorized legal guardian must be obtained prior to any research-related procedures. Within 21 days prior to hospital admission to implant the ICV access device, the following procedures will be performed:

- Informed consent
- Confirm diagnosis of CLN2 disease determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes.
- Blood for TPP1 enzyme activity and CLN2 gene analysis
- Hamburg CLN2 disease rating scale (motor, language, vision, and seizure subscales) with videotaping. Documentation of extent of disease progression with total score of 3-6 for motor/gait and language domains, as defined in the Ratings Assessment Guidelines, is required for study entry.
- Verify criteria for study entry
- Cranial MRI
- Complete physical examination, including medical history
- CLN2-specific QoL Questionnaire
- Pregnancy testing (in females of childbearing potential)
- After informed consent, assessment of SAEs related to protocol-imposed interventions and seizure history
- Concomitant medications, including anti-epileptic treatments

In order to ensure appropriate patients are enrolled in the study (including those with the necessary CLN2 ML scores at Screening), a confirmation of patient study eligibility will be provided to the Investigator by BioMarin. Surgery should not be performed until this approval is obtained. Information that must be provided for Sponsor approval includes (but is not limited to) patient age, results of TPP1 enzyme activity, results of CLN2 genotype testing (if available) and Screening ML score.

12.2 Surgery Visit

Following confirmation of patient eligibility and enrollment, study patients will be admitted to the hospital for surgical implantation of an ICV access device to the right lateral ventricle. An MRI will be performed prior to surgery to ensure proper planning and placement of the ICV access device. At minimum, subjects will be observed in a nursing-intensive

environment for 48 hours post-ICV device placement and after the start of the first drug infusion. The following procedures will also be performed:

- AE assessment, including ongoing seizure history
- Concomitant medication, including anti-epileptic treatments

Following ICV access device placement, subjects and their caregivers will be given written instructions providing details on signs and symptoms of concern for device complications and instruction on when to return to the site for device evaluation. An additional follow-up phone call will be conducted within 48 hours of inpatient discharge.

12.3 Baseline Visit and First Infusion

12.3.1 Baseline Visit

The following baseline values will be recorded within 2 days before the first infusion (which will occur at least 14 days from surgery and no more than 28 days after surgery):

- Height and body weight assessment
- Hamburg CLN2 disease rating scale (motor, language, vision, and seizure subscales) with videotaping
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities)
- EEG (standard awake)
- Cranial MRI
- CSF (TAb and NAb in all subjects) and serum (TAb, NAb, total IgE and drug-specific IgE in all subjects) for immunogenicity
- Complete physical examination
- Neurological examination
- Clinical laboratory testing (hematology, blood chemistry, and urinalysis)
- Modified Unified Batten Disease Rating Scale Involuntary Movement Scale (mUBDRS-Movement)
- Modified Unified Batten Disease Rating Scale Seizure Inventory (mUBDRS-Seizure)
- Optical coherence tomography
- PedsQL
- Denver II Developmental Scale
- CLN2-specific QoL Questionnaire

- Ophthalmologic assessments
- Visual acuity testing
    - All subjects will undergo Preferential Looking Testing. In addition, for those children who retain the cognitive function to adhere to testing, the Lea Vision Test or E Hook (or Tumbling E) Vision Test should also be performed during the same assessment. The subject must not be sedated at the time of visual acuity testing.
- AE assessment, including ongoing seizure history
- Concomitant medications, including anti-epileptic treatments

12.3.2 First Infusion

If done on the same day, assessments of function and QOL should be completed before MRI and blood sampling, which should precede infusion; blood samples may be collected when subjects are sedated for MRI.

12.3.2.1 First Infusion: Day 1

The following procedures will be performed on Day 1 of the first infusion:

- Continuous ECG monitoring (3- or 5-lead) will be performed for all subjects. The ECG should begin 15 (± 5 minutes) prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. In the event that the subject has already received the first infusion of BMN 190, the next infusion will be monitored as above.
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) 30 (±5) minutes after infusion end at the first infusion. In patients with present or past bradycardia, conduction disorders, or with structural heart disease, an ECG will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, 30 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end.
- CSF surveillance (cell count, protein, glucose, and culture)
- Device patency/infection
- Study drug infusion
- CSF and blood for disease-related biomarkers
- CSF and plasma for PK
- Vital signs (SBP, DBP, heart rate, oral body temperature, and respiration rate)
- Brief physical examination

- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern) and ongoing seizure history
- Concomitant medication assessment, including anti-epileptic treatments
- Post-infusion monitoring in an appropriate inpatient setting for a minimum of 24 hours

12.3.2.2 First Infusion: Days 2-6

The following procedures will be performed on Days 2-6 following the first infusion:

- Clinical laboratory testing (hematology, blood chemistry, and urinalysis) (Day 2)
- CSF surveillance (cell count, protein, glucose, and culture) (Day 6)
- Brief physical examination (Day 6)
- Device patency/infection (Day 6)
- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern) (each day) and ongoing seizure history
- Concomitant medication assessment (each day), including anti-epileptic treatments

Following inpatient discharge from the first infusion, a follow-up telephone call will be placed to parent/guardian within 48 hours.

12.4 Every 2 Weeks

The following assessments and procedures should be performed every 2 weeks (14 days) during the study. All study visits should occur every 2 weeks (14 days) from the date of the first infusion (±3 days). All assessments and procedures should be completed before study drug infusion unless specified otherwise. If done on the same day, QOL should be completed before MRI and blood sampling; blood samples may be collected when subjects are sedated for MRI.

For all visits, if no safety issues are observed, a subject may be discharged after 24 hours if medically stable. A follow-up phone call to the parent or legal guardian will be conducted ~48 hours after discharge to determine health status.

- Brief physical examination
- CSF surveillance (cell count with differential, protein, glucose, and culture)
- CSF for disease-related biomarker assays (Weeks 1-71)
- Device patency/infection assessment
- Study drug administration

- Vital signs (SBP, DBP, heart rate, oral body temperature, and respiration rate)
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) 30 (±5) minutes after infusion end at the first infusion. In patients with present or past bradycardia, conduction disorders, or with structural heart disease, an ECG will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, 30 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end.
- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern) and ongoing seizure history
- Concomitant medication assessment, including anti-epileptic treatments
- Telephone call to parent/guardian within 48 hours after visit

12.5 Every 4 Weeks

The following assessments and procedures should be performed every 4 weeks during the study. Where applicable, blood sampling may occur during sedation for MRI.

- Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis) (first 2 assessments only [Weeks 1-9])
- Hamburg CLN2 disease rating scale (motor, language, vision, and seizure subscales)

12.6 Every 8 weeks

The following assessments and procedures should be performed every 8 weeks during the study. Where applicable, blood sampling may occur during sedation for MRI.

- Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis) (for 5 assessments only [Weeks 17 to 49])
- CSF for disease-related biomarker assays (Weeks 79-145)
- Blood for disease-related biomarker assays (Weeks 1-49)

12.7 Every 12 Weeks

The following assessments and procedures should be performed every 12 weeks during the study. All assessments and procedures should be completed before study drug infusion unless specified otherwise. If done on the same day, assessments of function and QOL should be completed before MRI and blood sampling; blood samples may be collected when subjects are sedated for MRI.

- Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis) (starting at Week 61-145)
- Blood for disease-related biomarker assays (Weeks 61-145)
- Videotaping to accompany administration of the Hamburg CLN2 disease rating scale (motor, language, vision, and seizure subscales), which will be administered every 4 weeks.
    - Change in seizure activity (clinical [0 to 3 point Hamburg CLN2 rating scale seizure subscale])
- Visual acuity testing
    - All subjects will undergo Preferential Looking Testing every 12 weeks. In addition, for those children who retain the cognitive function to adhere to testing, the Lea Vision Test or E Hook (or Tumbling E) Vision Test should also be performed during the same assessment. Visual acuity testing can be performed either before or after the infusion (± 3 days), but should be performed at a time (relative to infusion) that can be repeated consistently between study visits. The subject must not be sedated at the time of visual acuity testing.
- Neurological examination
- CSF and serum sampling for immunogenicity
- mUBDRS-Movement
- mUBDRS-Seizure
- PedsQL
- Denver II Developmental scale
- CLN2-specific QoL Questionnaire

12.8 Every 24 Weeks

The following assessments and procedures should be performed every 24 weeks during the study:

- Height and body weight assessment
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities)
- Cranial MRI
- EEG (standard awake)
- Optical coherence tomography
- CSF and plasma for PK (Weeks 25, 49, and 97).

12.9 Every 48 Weeks

The following assessments and procedures should be performed every 48 weeks during the study:

- Complete physical examination
- Ophthalmologic assessments

12.10 Study Completion or Early Termination Visit

At Study Completion or Early Termination, subjects will return to the study site within 3 days. The following procedures will be completed:

- Hamburg CLN2 disease rating scale (motor, language, vision, and seizure subscales) with videotaping
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities)
- EEG (standard awake)
- Cranial MRI
- CSF surveillance (cell count, protein, glucose, and culture)
- CSF and blood for disease-related biomarker assays
- CSF and plasma for PK
- CSF and serum sampling for immunogenicity
- Vital signs (SBP, DBP, heart rate, oral body temperature, and respiration rate)
- Complete physical examination
- Height and body weight assessment
- Neurological examination
- Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Denver II Developmental scale
- Optical coherence tomography
- PedsQL
- Pregnancy testing (in females of childbearing potential)
- CLN2-specific QoL Questionnaire

- Visual acuity testing
    - All subjects will undergo Preferential Looking Testing. In addition, for those children who retain the cognitive function to adhere to testing, the Lea Vision Test or E Hook (or Tumbling E) Vision Test should also be performed during the same assessment. The subject must not be sedated at the time of visual acuity testing.
- Ophthalmologic assessments
- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern) and ongoing seizure history
- Concomitant medication assessment, including anti-epileptic treatments

Following the Study Completion Visit or Early Termination Visit, subjects who will not be continuing to receive BMN 190 in another setting (e.g., commercial use, participation in a registry, participation in another BMN 190 clinical study, etc.) should have their ICV access device removed. Removal of the device should occur no more than 4 weeks after the Study Completion Visit or ETV. All removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and all other devices (as described in the Pharmacy Manual) except for infusion pumps, should also be returned.

12.11 Device Safety Follow-Up

Subjects will return to the study site 4 weeks (±3 days) after removal of the ICV access device, when the following procedures will be completed:

- Hamburg CLN2 disease rating scale (motor, language, vision, and seizure subscales) (videotaping not required)
- Vital signs (SBP, DBP, heart rate, oral body temperature, and respiration rate)
- Brief physical examination (including close examination of the former device site to check for signs of infection, etc.)
- Serum sampling for immunogenicity
- Neurological examination
- Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern), including ongoing events at the time of the last dose or new events related to study drug.
- Concomitant medication assessment, including anti-epileptic treatments

Upon study completion or early termination, all patients will be given the opportunity to participate in a postmarketing registry that will assess long-term safety and efficacy of BMN 190 for patients receiving commercial drug.

The 4-week Device Safety Follow-Up Visit will be waived for subjects who do not undergo device removal because they will be continuing to receive BMN 190 in another setting (e.g., commercial use, participation in a registry, participation in another BMN 190 clinical study, etc.).

12.12 Safety Follow-Up

The Safety Follow-up visit is not required if a subject enrolls in an extension study or registry or otherwise continues to have access to BMN 190 within 6 months of the final infusion. For subjects who do not participate in an extension study or registry after the last dose of study drug, the 6 month safety follow visit will capture information regarding ongoing events at the time of the last dose or new events related to study drug. If required, subjects will return to the study site 6 months after the last study treatment, when the following procedures will be completed:

- Hamburg CLN2 disease rating scale (motor, language, vision, and seizure subscales) (videotaping not required)
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities)
- Serum sampling for immunogenicity
- Vital signs (SBP, DBP, heart rate, oral body temperature, and respiration rate)
- Complete physical examination
- Height and body weight assessment
- Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern), including ongoing events at the time of the last dose or new events related to study drug, and ongoing seizure history
- Concomitant medication assessment, including anti-epileptic treatments

12.13 Study Termination

The study will end after the last subject completes the last Safety Follow-Up visit. BioMarin reserves the right to discontinue the study any time for clinical or administrative reasons and to discontinue participation of an individual investigator or site for clinical or administrative reasons, including, but not limited to, poor enrollment or noncompliance with procedures of the protocol or GCP. In addition, the study may be terminated if, in the opinion of BioMarin, the safety of the study subjects may be compromised.

Upon study completion or early termination, all patients will be given the opportunity to participate in a postmarketing registry that will assess long-term safety and efficacy of BMN 190 for patients receiving commercial drug.

13 DATA QUALITY ASSURANCE

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

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

The designated clinical data management group will enter or transfer CRF data into a study database.

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

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Because the completeness of the data affects the integrity and accuracy of the final study analysis, every effort should be made to ensure complete, accurate, and timely data collection.

14.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written prior to final database lock that will provide details on the planned statistical analysis. If discrepancies exist between the statistical analysis as described in the protocol and the final SAP, the SAP will prevail.

14.1.1 Interim Analyses

No formal interim analyses are planned. As a single-arm, open-label study, study data will be available for review on an ongoing basis.

There will be no Data Monitoring Committee. However, BioMarin will convene a Data Review Board of internal and external experts to assist the Medical Monitor in assessing data.

Early stopping will be considered based on clinical judgment; no inferential stopping rules will be employed.

14.2 Primary Efficacy Analysis

The primary efficacy endpoint is the 0 to 6-point ML score on the Hamburg CLN2 rating scale. The primary measure of efficacy is the rate of CLN2 decline. This analysis will include patients with a baseline ML score < 6 points and patients with a ML score < 6 points post-baseline.

CLN2 disease rating scale scores will be evaluated relative to natural history data in untreated historical controls (data from a CLN2 disease patient registry and data from siblings with CLN2 disease, when available).

14.2.1 Secondary Efficacy Analyses

Time to disease manifestation will be assessed for asymptomatic patients. For all patients, an analysis of interest is time to first confirmed decline, defined as 2 consecutive CLN2 assessments (i.e., approximately 4 weeks apart) with scores less than the baseline CLN2 score.

The time to first confirmed decline is defined by the earlier of the 2 CLN assessments.

The 0-to-9 point Hamburg CLN2 scores (incorporating the motor, language, and vision domains) and the total 0-to-12 point Hamburg CLN2 scores (motor, language, vision, and seizure), will be presented descriptively.

The following variables obtained by MRI of the brain will be presented descriptively:

- Volume of CSF
- Volume of cortical gray matter
- Volume of white matter
- Whole brain apparent diffusion coefficient

Endpoints may be compared to natural history data in untreated historical controls (data from a CLN2 disease patient registry and data from siblings with CLN2 disease, when available).

14.2.2 Exploratory Analyses

The following domains/assessment instruments will be presented descriptively:

- mUBDRS-Movement
- mUBDRS-Seizure
- Seizure activity (clinical [0 to 3 point Hamburg CLN2 rating scale seizure subscale])
- Anti-epileptic treatment
- Retinal anatomy, as determined by optical coherence tomography
- PedsQL
- CLN2 health-related QoL
- Denver II Developmental scale
- EEG, standard awake
- Preferential Looking Test; Optional Lea Vision Test or E Hook (or Tumbling E) Vision Test
- CSF/ blood biomarkers

14.2.3 Immunogenicity Analysis

Immunogenicity tests will be performed using validated immunogenicity assays. Routine immunogenicity tests will include total antibody (TAb) and neutralizing antibody (NAb) in the serum and CSF. NAb testing will not be performed if the TAb is negative. Incidence and titer summary statistics will be provided for serum TAb, CSF TAb, serum Nab, and CSF NAb in table format and will include mean, median, standard deviation, and

minimum/maximum titer values at each study visit. Potential impact of anti-drug antibodies on efficacy and safety will be explored.

In the event of serious or severe (≥Grade 3) hypersensitivity AE, blood samples will be collected within 1 hour of the event to assess C4, serum tryptase, and total IgE. A second blood sample will be collected no sooner than 8 hours after the event (or before the next infusion) for drug-specific IgE testing. Potential associations between immunogenicity results and hypersensitivity adverse events will be analyzed.

14.3 Pharmacokinetic Analysis

The following parameters will be evaluated by non-compartmental analysis:

- Area under concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
- Area under concentration-time curve from 0 to the time of last measurable concentration (AUC_{0-t})
- Maximum observed concentration (C_{max})
- Time to reach C_{max} (T_{max})
- Elimination half-life ($t_{½}$)
- Apparent clearance of drug (CL/F)
- Apparent volume of distribution based on terminal phase (V_z/F)

14.4 Safety Analysis

Safety analysis will be descriptive.

All AEs will be coded by BioMarin using the current version of MedDRA to assign system organ class and preferred term classification to events and diseases, based on the original terms entered on the CRF. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment, and severity.

Concomitant medications will be coded using World Health Organization Drug Dictionary and summarized.

Clinical laboratory data will be summarized in terms of observed values and changes from Baseline. Lab data will also be summarized relative to categorical reference ranges (e.g., lab normal ranges and/or CTCAE grade).

Vital signs will be summarized in terms of observed values and changes from Baseline.

ECGs will be summarized in terms of investigator overall interpretation, abnormal findings, and quantitative intervals (QTcF, etc.).

14.5 Determination of Sample Size

Sample size was determined on the basis of clinical judgment. Statistical power was not a consideration.

14.6 Changes in the Conduct of the Study or Planned Analyses

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

With the exception of minor administrative or typographical changes, the IRB/IEC/REC must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REC prior to their implementation.

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

15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet to assess available patient safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of patient safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

The DRB will consist of 3 members: the BioMarin medical monitor, a representative from BPV, and one study investigator. The DRB will meet on a quarterly basis, for the first year of the study and ad hoc thereafter. The DRB will be provided with statistical support and may access external clinical opinion.

16 COMPENSATION, INSURANCE, AND SUBJECT INJURY

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

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

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic case report forms (eCRFs) 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representative) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If 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 CRFs is accurate and complete. The Data Manager, or designee, will then set the status of the forms, visits, and the entire casebook to Locked. Upon completion of the CSR, an electronic copy of each site's casebooks will be copied to a compact disk (CD) and 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 GCP Compliance Department (or designee) 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 auditors have access to 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 study files. The investigator and/or 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 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 US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. The investigator and/or institution should retain subject identifiers for at least 15 years after 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 and/or institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of BioMarin to inform the investigator and/or institution 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 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 data from this study will be described in the Clinical Trial Agreement between BioMarin and the investigator and/or institution. Consideration for authorship of all publications will be based on compliance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals ("Uniform Requirements") of the International Committee of Medical Journal Editors (http://www.icmje.org/ethical_1author.html) 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 GCP, the investigator will ensure that:

- S/he 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.
- S/he will personally conduct or supervise the study.
- S/he will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and s/he will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and/or ICH sections 2.9 and 4.8 are met. As well, IRB/IEC review and approval requirements in 21 CFR Part 56 and/or ICH section 2.6 are met.
- S/he will report to the sponsor AEs that occur in the course of the investigation in accordance with 21 CFR 312.64 and/or ICH section 4.11.
- S/he 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.
- S/he will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and/or ICH section 4.9 and to make those records available for inspection in accordance with 21 CFR 312.68 and/or ICH section 4.9.7.
- S/he will ensure that the IRB/IEC/REC 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. S/he 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/REC. Additionally, he or she will not make any changes in the research without IRB/IEC/REC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- S/he 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, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Pediatric Patients < 18 years of age with CLN2 Disease

Protocol Number: 190-203 Amendment 6

I have read the forgoing protocol amendment 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:

Medical Monitor Signature Date

Printed Name: PI

24 APPENDICES

Appendix 1: Adapted CLN2 Disease Rating Scale

Hamburg LINCL Scale (Steinfeld, 2002), adapted for multicenter use			**Weill Cornell LINCL Scale** (Dyke, 2012), adapted for multicenter use		
Motor / Gait	3	Grossly normal gait. No prominent ataxia, no pathologic falls			
	2	Independent gait, as defined by ability to walk without support for 10 steps. Will have obvious instability, and may have intermittent falls.			
	1	Requires external assistance to walk, or can crawl only.			
	0	Can no longer walk or crawl.			
Language	3	Apparently normal language. Intelligible and grossly age-appropriate. No decline noted yet.			
	2	Language has become recognizably abnormal: some intelligible words, may form short sentences to convey concepts, requests, or needs. This score signifies a decline from a previous level of ability (from the individual maximum reached by the child).			
	1	Hardly understandable. Few intelligible words			
	0	No intelligible words or vocalizations			
Vision	3	Grossly normal. Appears to recognize multiple objects and reacts appropriately (reaches for a toy, etc.)	Myoclonus	3	No myoclonus, involuntary movements. Babinski not present
	2	Apparent difficulty seeing some objects. May be able to discern large objects, moving objects, but vision is clearly impaired. This score signifies a decline from a previous level of ability.		2	One finding: (myoclonus) (chorea, dystonia, tremor, athetosis) (Babinski present)
	1	Reacts only to light		1	Two findings: (myoclonus) (chorea, dystonia, tremor, athetosis) (Babinski present)
	0	No reaction to light		0	Myoclonus, involuntary movements, and Babinski present

Seizures (grand mal)	3	No seizures in 12-week period	Feeding	3	No swallowing dysfunction
	2	1 to 2 seizures in 12-week period		2	Mild swallowing dysfunction but tolerates most food / drinks
	1	3 seizures in 12-week period (1 per 4 weeks)		1	Moderate swallowing dysfunction: difficulty with many foods
	0	> 3 seizures in 12-week period (> 1 per 4 weeks)		0	Gastrostomy tube dependent

25 PROTOCOL AMENDMENT TEXT REVISIONS

The following is a detailed summary of significant protocol revisions corresponding with the rationale for changes (Page 2-5); added text is underlined and deleted text is ~~struck~~. Additional administrative changes have been made for consistency and clarity throughout this amendment and are reflected in the protocol body.

<table>
<tr><th>Section</th><th>Revision</th><th>Rationale for Change</th></tr>
<tr><td>Table 9.1.1/SOE</td><td>• Restored row for Ophthalmologic Assessments that was inadvertently removed in Protocol Amendment 5.
<table>
<tr><td>Assessments and Events</td><td>Screening[a]</td><td></td><td colspan="2">Baseline/ First Infusion (≤ 2 days prior to first dose)</td><td>Treatment Period Weeks 1 to 144</td><td>Study Completion/ Early Termination</td><td>Device Safety Follow-Up</td><td>Safety Follow-Up</td></tr>
<tr><td>Ophthalmologic assessments</td><td></td><td></td><td>X</td><td></td><td>Q48W</td><td>X</td><td></td><td></td></tr>
<tr><td>Visual acuity testing[u]</td><td></td><td></td><td>X</td><td></td><td>Q12W</td><td>X</td><td></td><td></td></tr>
</table></td><td>1</td></tr>
<tr><td>12.3.1/ Baseline Visit</td><td>• Ophthalmologic assessments
• Visual acuity testing
o All subjects will undergo Preferential Looking Testing. In addition, for those children who retain the cognitive function to adhere to testing, the Lea Vision Test or E Hook (or Tumbling E) Vision Test should also be performed during the same assessment. The subject must not be sedated at the time of visual acuity testing.</td><td>1</td></tr>
<tr><td>12.9/ Every 48 Weeks</td><td>• Complete physical examination
• Ophthalmologic assessments</td><td>1</td></tr>
<tr><td>12.10/ Study Completion or Early Termination Visit</td><td>• Visual acuity testing
o All subjects will undergo Preferential Looking Testing. In addition, for those children</td><td>1</td></tr>
</table>

	who retain the cognitive function to adhere to testing, the Lea Vision Test or E Hook (or Tumbling E) Vision Test should also be performed during the same assessment. The subject must not be sedated at the time of visual acuity testing. • **Ophthalmologic assessments**	