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Long-Term Open-Label Extension Study of Cerliponase Alfa in Children with CLN2 Disease: Safety and Efficacy After >5 Years of Therapy

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Abstract:	BACKGROUND: Cerliponase alfa is a recombinant human tripeptidyl peptidase 1 (TPP1) enzyme replacement therapy for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) caused by mutations in the TPP1 gene. The aim of this study was to determine the long-term safety and efficacy of intracerebroventricular (ICV) cerliponase alfa in children with CLN2 disease. METHODS: This analysis includes cumulative data from a 48-week primary study (NCT01907087) and a completed 240-week open-label extension with 6-month safety follow-up (NCT02485899), conducted at 5 hospitals in Germany, Italy, the UK, and the USA between 13 September 2013 and 10 December 2020. Children aged 3-16 years with CLN2 disease confirmed by genetic analysis and enzyme testing were eligible for inclusion. Historical untreated controls with CLN2 disease in the DEM-CHILD database were used as a comparator group. Treatment was ICV infusion of 300 mg cerliponase alfa every 2 weeks. The primary efficacy outcome was time to an unreversed 2-point decline or score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale. FINDINGS: Twenty-four participants were enrolled in the primary study (15 female, 9 male); 23 participants enrolled in the extension and received 300 mg cerliponase alfa for a mean (range) of 272.1 (162.1–300.1) weeks: 17 participants completed the

	extension and 7 discontinued prematurely. Treated patients were significantly less likely than historical untreated controls to have an unreversed 2-point decline or score of 0 in the combined motor-language domains (hazard ratio, 0.14; 95% confidence interval, 0.06 to 0.33; p<0.0001). All participants experienced ≥1 adverse event (AE) and 21 (88%) experienced a serious AE; 9 participants experienced ICV device-related infections with 9 events in 6 participants resulting in device replacement. There were no study discontinuations because of an AE. There were no deaths and treated patients were significantly less likely to die than historical controls. INTERPRETATION: Cerliponase alfa treatment over a period of >5 years was seen to confer a clinically meaningful slowing of motor and language function decline in children with CLN2 disease. Although our study is limited by the lack of a contemporaneous control group, the results provide critical insights into the outcomes of long-term treatment. FUNDING: BioMarin Pharmaceutical Inc.

Long-Term Open-Label Extension Study of Cerliponase Alfa in Children with CLN2 Disease: Safety and Efficacy After >5 Years of Therapy

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ABSTRACT

BACKGROUND: Cerliponase alfa is a recombinant human tripeptidyl peptidase 1 (TPP1) enzyme replacement therapy for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) caused by mutations in the *TPP1* gene. The aim of this study was to determine the long-term safety and efficacy of intracerebroventricular (ICV) cerliponase alfa in children with CLN2 disease.

METHODS: This analysis includes cumulative data from a 48-week primary study (NCT01907087) and a completed 240-week open-label extension with 6-month safety follow-up (NCT02485899), conducted at 5 hospitals in Germany, Italy, the UK, and the USA between 13 September 2013 and 10 December 2020. Children aged 3-16 years with CLN2 disease confirmed by genetic analysis and enzyme testing were eligible for inclusion. Historical untreated controls with CLN2 disease in the DEM-CHILD database were used as a comparator group. Treatment was ICV infusion of 300 mg cerliponase alfa every 2 weeks. The primary efficacy outcome was time to an unreversed 2-point decline or score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale.

FINDINGS: Twenty-four participants were enrolled in the primary study (15 female, 9 male); 23 participants enrolled in the extension and received 300 mg cerliponase alfa for a mean (range) of 272·1 (162·1–300·1) weeks: 17 participants completed the extension and 7 discontinued prematurely. Treated patients were significantly less likely than historical untreated controls to have an unreversed 2-point decline or score of 0 in the combined motor-language domains (hazard ratio, 0·14; 95% confidence interval, 0·06 to 0·33; $p<0·0001$). All participants experienced ≥1 adverse event (AE) and 21 (88%) experienced a serious AE; 9 participants experienced ICV device-related infections with 9 events in 6 participants resulting in device replacement. There were no study discontinuations because of an AE. There were no deaths and treated patients were significantly less likely to die than historical controls.

INTERPRETATION: Cerliponase alfa treatment over a period of >5 years was seen to confer a clinically meaningful slowing of motor and language function decline in children with CLN2 disease. Although our study is limited by the lack of a contemporaneous control group, the results provide critical insights into the outcomes of long-term treatment.

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RESEARCH IN CONTEXT

Evidence before this study

We conducted a PubMed search for clinical trials published between 1 January 1966 and 24 May 2023, using the text word search terms "CLN2 disease," "neuronal ceroid lipofuscinosis type 2," or "Batten disease", and "cerliponase alfa" without language restriction. To date, the safety, efficacy, and immunogenicity of cerliponase alfa have been assessed in a completed multicentre, single-arm, dose-escalation clinical study (NCT01907087, EudraCT 2012-005430-11) after all participants had received at least 48 weeks of 300 mg dosing and an interim analysis (an additional 48 weeks of data) of a 240-week extension study (NCT02485899, EudraCT 2014-003480-37). Compared with historical controls, patients treated with the recommended 300 mg cerliponase alfa every 2 weeks for at least 96 weeks experienced a statistically significant slowing of decline in motor and language function. Adverse events, including seizures, pyrexia, vomiting, device-related infections, and hypersensitivity reactions, were shown to be manageable and did not result in treatment discontinuation. These data represent a clinically meaningful preservation of motor and language function and an acceptable risk profile and have increasingly led to cerliponase alfa becoming the standard of care for children with CLN2 disease, where this treatment is available.

Added value of this study

This report presents final long-term outcomes (>5 years of treatment) based on cumulative data from the primary and extension studies of safety and efficacy of cerliponase alfa in children with CLN2 disease. Participants in the study ranged in age between 3.1 and 8.9 years at the time of enrolment. After >5 years of follow-up in the long-term extension study, all patients had reached the age at which disease progression would be expected to be very advanced, and thus the data presented here provide additional information about the efficacy of treatment through the expected phase of most rapid decline. Moreover, many patients had reached an age exceeding the typical life expectancy for untreated patients, and a significant impact of treatment on mortality was observed.

Implications of all the available evidence

Taken together, the data show that long-term intracerebroventricular administration of 300 mg cerliponase alfa every 2 weeks in children with CLN2 disease slows decline in critical motor and language functions compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these did not result in treatment discontinuation, and immunogenicity does not appear to be a limiting factor with respect to either safety or efficacy.

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) is a rare, rapidly progressive paediatric neurodegenerative disease caused by mutations in the tripeptidyl peptidase 1 *TPP1* gene resulting in TPP1 enzyme deficiency.[1,2] Deficient activity of TPP1 is associated with intracellular accumulation of lysosomal storage materials and neuronal cell death.[1] Children with CLN2 disease appear healthy at birth and often show delayed language acquisition before other symptoms manifest, typically at age 2-4 years with seizures and ataxia.[1,3,4] The classic late-infantile disease phenotype is characterized by loss of motor and language functions beginning at around 3 years of age and includes language regression and eventual complete loss of expressive language; new onset or worsening ataxia and complex movement disorders resulting in complete loss of independent mobility; worsening epilepsy, which may become intractable; progressive loss of ability to swallow; progressive dementia; deterioration of vision leading to blindness; and death by adolescence.[1,5,6]

In 2017, the European Medicines Agency and the United States Food and Drug Administration approved cerliponase alfa (Brineura; BioMarin Pharmaceutical Inc., Novato, CA) enzyme replacement therapy for treatment of CLN2 disease. Efficacy of cerliponase alfa was demonstrated by comparing changes in the combined motor and language domains of the CLN2 Clinical Rating Scale in treated patients with those in untreated historical controls enrolled in the DEM-CHILD NCL database.[7] Motor and language function are hallmarks of CLN2 disease severity and can be reliably measured by clinical raters: each domain of the CLN2 Clinical Rating Scale is scored from 0 to 3, with a score of 3 representing normal function and a score of 0 representing complete loss of function (Table S1). Compared with untreated historical controls, patients treated with 300 mg of cerliponase alfa for at least 96 weeks were shown to be less likely to experience an unreversed 2-point decline or score of 0 in the combined motor and language domains (hazard ratio [HR], 0·08; 95% confidence interval [CI], 0·02 to 0·23; $p<0·0001$) and had a lower mean rate of decline in motor and language function.[7] Common adverse events (AEs) in treated patients included seizures, pyrexia, vomiting, and hypersensitivity reactions.

We present cumulative data from the primary and completed open-label extension studies to assess the safety and efficacy of cerliponase alfa in children with CLN2 disease over >5 years of treatment.

METHODS

Study Design

Study 190-201 was a 48-week, single-arm, open-label, multicentre, dose-escalation study of intracerebroventricular (ICV) cerliponase alfa, conducted between September 2013 and November 2015 at 5 tertiary care hospitals (1 each in Germany, Italy, and the United States; and 2 in the United Kingdom).[7] Upon completion of the 48-week primary study, participants with a combined motor-language score of >0 on the CLN2 Clinical Rating Scale (Table S1) were eligible to enroll in study 190-202, an open-label extension study conducted between 02 February 2015 and 10 December 2020. Participants continued to receive 300 mg of ICV cerliponase alfa every 2 weeks for 240 weeks (Figure S1). A safety follow-up visit was performed 6 months after completion of the 240-week dosing period. Cumulative data from both the primary and extension studies are presented.

The primary and extension studies were registered at clinicaltrials.gov (NCT01907087 and NCT02485899) and EudraCT (2012-005430-11 and 2014-003480-37). See the Supplementary Material for the extension study protocol and statistical analysis plan.

Participants

Participants eligible to enroll in the primary study were between the ages of 3 and 15 years and had a diagnosis of CLN2 disease confirmed by deficient TPP1 enzyme activity and genetic analysis. Additional inclusion and exclusion criteria can be found in the Supplementary Material.

Written informed consent from a parent or legal guardian of each participant was obtained, and assent was obtained from the participant, if appropriate. The studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by all relevant institutional ethics boards.

The historical control group consisted of CLN2 patients who were enrolled in the DEM-CHILD NCL patient database and who were diagnosed and followed in NCL specialty centers in Hamburg, Germany and Verona, Italy.[4,8]

Procedures

Cerliponase alfa was administered via infusion (at a rate of 2·5 ml/ hour for 4 hours) through an ICV reservoir surgically implanted into the lateral cerebral ventricle. Following the dose-escalation phase of the primary study and during the extension study, participants received 300 mg cerliponase alfa every 2 weeks. Due to the potential for hypersensitivity reactions, prophylactic antihistamine and/or antipyretic could be administered at the investigator's discretion approximately 30 minutes before each infusion. During the extension study, the CLN2 Clinical Rating Scale was administered every 8 weeks. Safety assessments included brief physical exam, AEs, concomitant medication use, vital signs, and cerebrospinal fluid (CSF) surveillance every 2 weeks; clinical laboratory tests, neurologic exam, visual acuity tests, and CSF/serum collection for immunogenicity tests every 12 weeks; and MRI, quality of life assessments, developmental assessments, electrocardiograms, and electroencephalograms every 24 weeks. Complete physical examination was performed every 48 weeks. The attribution of AEs to the study drug or device was determined by the investigator and was not adjudicated. Wherever possible, AEs were recorded with a diagnosis as the AE term rather than as a series of terms relating to a diagnosis.

Validated assays were used to assess serum and CSF anti-drug total antibody (TAb) and CSF neutralizing antibody (NAb) titers.[9] NAb testing was performed on baseline CSF samples and on subsequent CSF samples found to be TAb positive. Drug-specific immunoglobulin E (IgE) testing was performed on serum samples collected in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or hypersensitivity adverse event (HAE) of Grade 3 or higher. See appendix for additional details regarding immunogenicity monitoring methods.

Outcomes

The primary efficacy outcome of study 190-202 was the time to first unreversed 2-point decline or unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale, comparing treated patients with historical untreated controls (see Supplementary Material for details regarding the scale and its assessment).[10-12] An unreversed 2-point decline was defined as a decline that had not returned to within 1 point of baseline score by the last

assessment. The same principal investigator, or a qualified physician designated by the principal investigator, who was continuously trained on the CLN2 Clinical Rating Scale, assessed subjects at their study site.

Pre-specified supportive analyses of the primary efficacy outcome included assessment of time to first unreversed 2-point decline or a score of 0 on the separate motor and language domains of the CLN2 Clinical Rating Scale; time to unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale; rate of decline in the combined motor-language score; and change from baseline in the combined motor-language score, total CLN2 Clinical Rating Scale score (motor, language, vision, seizure domains), and individual domain scores. For each, outcomes in treated patients were compared with historical untreated controls.

The secondary efficacy endpoint was brain atrophy, evaluated by volumetric MRI in treated patients considering one or more of the following: whole brain volume, percent cerebrospinal fluid, percent gray matter, percent white matter, whole brain apparent diffusion coefficient and cortical thickness. Data on whole brain percent gray matter is presented here as it is the most well described in published natural history studies of CLN2 disease patients.[13] Analyses of additional MRI parameters, pooling data from multiple studies, are ongoing and will be reported separately.

Exploratory efficacy endpoints were survival, CSF and plasma biomarkers, developmental milestones (Denver II Development Scale), anti-epileptic treatment, Quality of Life (Pediatric Quality of Life Inventory [PedsQL] Parent Report for Toddlers and Parent Family Impact; CLN2 disease-based Quality of Life), retinal anatomy using optical coherence tomography, visual acuity, and electroencephalograms. Analyses of survival, quality of life, and developmental milestone data are presented in the Supplementary Materials. Data collected on CSF and plasma biomarkers, anti-epileptic treatment, retinal anatomy, visual acuity, and electroencephalograms are not reported here. Retinal anatomy and visual acuity assessments were only conducted in the extension study and were added as part of a protocol amendment, limiting their utility for evaluating progression of retinal disease due to lack of baseline and data over the first year of treatment. Data on neurofilament light (NF-L) as a potential biomarker for CLN2 disease collected in the primary and extension studies have been published elsewhere.[14] Data on other outcomes are the subject of ongoing analyses.

Statistical Analysis

No formal sample size calculations were performed: sample size for the primary study was based on the ultra-rare nature of CLN2 disease.

All participants who received more than 1 dose of cerliponase alfa were included in efficacy analyses and were compared with evaluable untreated historical controls enrolled in the DEM-CHILD NCL registry.[4,8] Baseline measurement for treated patients was defined as the last observation preceding the first administration of a 300 mg dose of cerliponase alfa. For patients in the historical control cohort, baseline score on the combined motor-language scale was defined as the first score of less than 6 occurring at the age of 36 months or more; the age at baseline assessment was calculated as the midpoint of the age range of assessments at the time this score was obtained.

Kaplan-Meier methods and the Cox proportional-hazards model were used to compare the time to unreversed 2-point decline or a score of 0 and the time to unreversed score of 0 on the

combined motor-language domains for treated patients and historical controls. Follow-up was from baseline to time of unreversed 2-point decline or score zero (event) or time of last CLN2 clinical rating scale assessment (censoring). The Cox model included baseline combined motor-language score, age, genotype (common alleles), and sex as covariates. Similar analyses were performed to examine differences in the motor and language domain scores alone, as well as time to score of 0 on the combined motor-language domains.

Rate of decline in the combined motor-language score was calculated as the change from baseline to last assessment with a score of more than 0 divided by the length of follow-up and compared between treated patients and historical controls using a 2-sample t-test based on unequal variances. Change from baseline in the CLN2 Clinical Rating Scale score was calculated for 2 domains (motor and language; range 0-6), 4 domains (motor, language, vision, and seizures; range, 0-12), and for individual domains (for each, range 0-3) and compared between treated patients and historical controls. Confirmatory analyses of change from baseline were also performed in matched cohorts (see Supplementary Methods).

Changes in brain volume for treated patients, assessed by non-contrast whole brain MRI, were summarized by timepoint as absolute and percent changes from baseline.

Methods used for analyses of exploratory efficacy endpoints (mortality, quality of life, and developmental milestones) are described in the Supplementary Materials.

Safety data presented include all AEs reported in the primary and extension studies from the last observation preceding device implantation until 6 months after either the last administration of study drug or early termination visit. Relationships between immunogenicity and safety or efficacy endpoints were explored for TAb-negative and TAb-positive patients using box-plots. Seizure AEs mapping to the Convulsions Standardized MedDRA Query (SMQ) were assessed for consecutive 24-week intervals.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Role of the Funding Source

The study was funded by BioMarin Pharmaceutical, Inc. The funder designed the study with input from the investigators and health authorities, and provided the study medication. Data were collected by the investigators and were entered into an electronic data capture system maintained by the funder. Data were analyzed by the funder according to a prespecified statistical analysis plan agreed upon with the study investigators; interpretation of the study data was performed by the funder in conjunction with the investigators. Authors employed by the funder (JCP, PS, SB, ACherukuri) contributed to the development of the manuscript in conjunction with the other authors. Assistance with manuscript preparation was provided by a medical writer employed by the funder.

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RESULTS

Participants were screened and enrolled in the primary study between 13 September 2013 and 22 December 2014. All 24 participants who enrolled in the primary study were evaluated for safety. One participant withdrew from the primary study at the parents' request after receiving 1 dose of the study drug due to an inability to comply with study procedures, and was excluded from efficacy analyses. Incidence rates for AEs may therefore be slightly under-reported due to the very early termination of 1 participant. Of the 23 participants who received more than 1 dose

of cerliponase alfa, all completed the primary study and enrolled in the extension study. Seventeen of the 23 participants who enrolled in the extension study completed the planned follow-up. Six participants withdrew from the extension study: 4 due to relocation or switch to commercial therapy and 2 due to meeting study stopping criteria, having a score of 0 in the combined motor-language domains assessed at consecutive study visits. For participants who withdrew, all data up until the last available assessment were included for analysis. The database of untreated historical controls contained 69 individuals of whom 42 satisfied the criteria for comparability to the treated population.

Demographic and clinical characteristics of enrolled participants are summarized in Table 1. The population included 9 males (37.5%) and 15 (62.5%) females. The mean (SD) age at the time of enrollment in the primary study was 4·9 (1·3) years and the mean (SD) score on the combined motor-language domains of the CLN2 Clinical Rating Scale at 300 mg baseline was 3·5 (1·2), (range, 1 to 6). The safety population (n=24) was followed for a mean (SD) treatment duration of 263·2 (67·9) weeks (range, 0·1 to 309·1). The 23 participants who enrolled in the extension study and were evaluated for efficacy received 300 mg of cerliponase alfa for a mean (SD) of 272·1 (37·4) weeks (range, 162·1–300·1). A total of 3142 infusions were administered across both studies, with 3113 infusions at the 300 mg dose; the mean (SD) number of infusions per participant at any dose was 130·9 (33·5).

Treated patients were significantly less likely than historical controls to have an unreversed 2-point decline or a score of 0 in the combined motor-language domains (Figure 1A; HR, 0·14; 95% CI, 0·06 to 0·33; p<0·0001). The median (95% CI) time to event was 272 weeks (lower CI, 199 weeks; upper CI not estimable) in treated patients compared to 49 weeks (95% CI, 39 to 58) in historical controls. Similar results were observed for the motor and language domains individually (Figure S2A and S2B, respectively). Treated patients were also significantly less likely than historical controls to reach an unreversed score of 0 in the combined motor-language domains, representing complete loss of ability to ambulate and communicate (Figure 1B; HR, 0·02; 95% CI, 0·00 to 0·08; p<0·0001). The median time to reach an unreversed score of 0 was 109 weeks (95% CI, 90 to 129) in historical controls; only 3 treated patients reached an unreversed score of 0 by study completion and the median time to score 0 was not estimable. All 3 patients who reached a score of 0 had a baseline motor-language score of 3: one reached a score of 0 only at the study completion visit (week 288), one patient reached a score of 0 at week 264, and one patient at week 193.

The estimated mean (SD) rate of decline in the combined motor-language score was 0·38 (0·50) points per 48 weeks among treated patients (range: 0·00 to 2·18) and 2·13 (0·95) points per 48 weeks among historical controls (range: 0·45 to 4·27), a mean difference of 1·75 points (95% CI, 1·39 to 2·11; p<0·0001). After adjustment for baseline covariates (age, baseline motor-language score, sex, and genotype), the rate of decline was 0·64 (0·09) points per 48 weeks among the treated patients and 1·99 (0·14) points per 48 weeks among historical controls, a mean difference of 1·35 points (95% CI, 0·99 to 1·71; p<0·0001).

Combined motor-language score was seen to decline rapidly in the historical controls (Figure 1C), with scores approaching 0 by week 145. Treated patients showed a gradual decline from baseline over time reaching a mean (SD) score of 2·8 (1·43) points by week 145 and 1·8 [1·07] by week 313. Similarly, a rapid decline in total CLN2 Clinical Rating Scale score (motor, language, vision, and seizure domains) was observed for historical controls compared with a

more gradual decline in treated patients (Figure 1D). Similar results were attained in analyses performed in matched cohorts (see supplemental results; Figures S3-S5).

Data on change from baseline in individual CLN2 Clinical Rating Scale domain scores are shown in Figure S6 and Table S2. Vision domain score was seen to decline in both groups, albeit more rapidly in the historical controls (Figure S6). Treated patients showed a mean decline of 1.4 points from baseline to week 289 compared with a decline of 2.3 points for historical controls (Table S2). The seizure domain score provides an assessment of the frequency of tonic-clonic seizures: mean (SD) seizure domain score increased from 1·7 (1·2) at baseline to 2·4 (0·8) at week 289 in treated patients but decreased from 1·7 (1·1) to 0·7 (1·2) in historical controls, indicating declining frequency of seizures in treated patients and increasing frequency of seizures in historical controls (Table S2 and Figure S6).

Mean percentage change from baseline in total gray matter volume of treated patients, assessed by MRI, is shown in Figure 2. The mean absolute change from baseline to week 49 (end of the primary study) was -9·7%. At week 145, the observed change from baseline was -13·4% and, as of the last observation in the study, the change from baseline was -14·7%.

Data on exploratory efficacy endpoints (mortality [Figure S7], quality of life [Tables S3 and S4], and developmental milestones [Table S5]) are presented in the Supplementary Materials.

All participants experienced at least 1 AE (Table 2 and Table S6). Most AEs were Grade 1 or 2 in severity; 18 participants (75%) had at least one AE of Grade 3 and 3 participants (13%) had a Grade 4 AE. Grade 4 AEs were blindness, pyelonephritis, and status epilepticus. Fifteen participants experienced 52 AEs leading to dose interruptions; no AEs led to dose reduction. There were no deaths and no study discontinuations because of an AE. A total of 237 AEs in 23 participants were considered related to study drug; the most common drug-related AEs were pyrexia (127 events in 11 participants), hypersensitivity (16 events in 10 participants), seizure (14 events in 9 participants), vomiting (15 events in 6 participants), and epilepsy (4 events in 4 participants).

Overall, 107 serious adverse events (SAEs) were reported in 21 participants (88%) (Table 2 and Table S7). A total of 12 SAEs in 8 participants were considered related to study drug; the most common drug-related SAEs were hypersensitivity (9 events in 7 participants), infusion-associated reaction (2 events in 1 participant), pleocytosis (1 event in 1 participant).

Eighteen participants (75%) had a total of 56 hypersensitivity AEs (HAEs; Table S8); 29 were Grade 1, 19 were Grade 2, and 8 were Grade 3. There were no AEs of anaphylaxis or anaphylactoid reactions according to the criteria of the US National Institute of Allergy and Infectious Diseases. Twenty-one participants (88%) had a combined 79 device-related AEs (Table S9): the most common were device-related infections (15 events in 9 participants) and device end-of-service events, representing prophylactic replacement of the ICV device (13 events in 13 participants). A total of 29 device-related SAEs were reported in 16 participants, including 12 device-related infections in 7 participants. A total of 14 device-related AEs in 7 participants led to ICV device replacement (2 participants had 3 device replacement; 2 participants had 2 replacements, and 3 participants had a single replacement): device-related infection (9 events in 6 participants), device leakage (2 events in 2 participants), device deployment issue (2 events in 2 participants), and device malfunction (1 event in 1 participant). Device-related infections were managed with intravenous antibiotics, with the specific agent

used being determined based on the organism identified. In all cases, the ICV device was successfully replaced without complication and without discontinuation of study drug.

A total of 7 participants (29%) experienced 15 cardiovascular events (most common were: bradycardia, 4 events; hypotension, 4 events; hematoma, 2 events) and 23 participants (96%) experienced 693 events mapping to the convulsions Standardized MedDRA Query (Table S10). No events of hydrocephalus, meningitis, or unexpected rapid decline in motor-language score were reported. The proportion of participants who reported ≥1 event of convulsions as an AE declined from 88% (n=21) during weeks 0-24, reaching a nadir of 26% (n=23) during weeks >144 to 168, before increasing to 59% (n=13) in weeks >216 (Figure S8).

The anti-drug antibody (ADA) response in all participants by time on treatment is displayed for CSF TAb (Figure S9A) and serum TAb (Figure S9B). CSF TAb response was detected in 10 participants (42%); earliest time to onset was 13 weeks. CSF TAb titers returned to undetectable levels in 9 out of 10 ADA positive participants by the end of the study. Serum TAb response was detected in 19 participants (79%); titers were sustained in 12/19 (63%), declined in 5/19 (26%), and reverted to undetectable in 2/19 (11%) by the end of the study. Low titer NAb were detected in the CSF of 3 participants (13%) at a single visit. Change from baseline in the combined motor-language score was comparable between CSF TAb-negative and TAb-positive participants (Figure S10). Six participants reported 8 Grade 3 HAEs; however, no association was found between serum ADA titer and either the incidence or severity of HAEs (Figure S11A and S11B, respectively). Serum samples collected from all participants reporting Grade 3 HAEs were tested and found negative for drug-specific IgE.

DISCUSSION

Intracerebroventricular cerliponase alfa is the first disease-modifying treatment approved for CLN2 disease. Treatment with 300 mg cerliponase alfa every other week for at least 96 weeks was shown to result in meaningful preservation of motor and language function, with acceptable safety and tolerability,[7] and cerliponase alfa has increasingly become the standard of care for children with CLN2 disease, where available.[15] In this report, we confirm that slowing of clinical disease progression is maintained through >5 years of treatment, with expected but manageable safety events. After completion of the 240-week treatment period of the study, participants were not required to continue on treatment. However, all who completed the treatment period did indeed continue to receive infusions and remained on treatment at the time of the 6-month safety follow-up visit.

After receiving cerliponase alfa for at least 162 weeks at the 300 mg dose, treated patients were found to be less likely than historical untreated controls to experience an unreversed 2-point decline or a score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale. The mean (SD) rate of decline in the combined motor-language domain score was 1·75 points/48 weeks lower for treated patients than for historical controls. Rates of decline were comparable to those reported after 96 weeks of treatment suggesting that attenuation of disease progression is maintained. Although a decline in motor-language score was still seen in treated patients, the attenuation relative to historical controls was clinically meaningful: by the end of study, motor-language score in treated patients had declined by approximately 1.5 points to a median score of 2: at this level children require assistance to walk and have limited language. In comparison, for historical controls, the median time to reach a motor-language score of 0,

representing complete loss of ambulation and ability to communicate through speech, was 109 weeks.

Seizures are a predominant feature of CLN2 disease and remain a significant burden throughout disease progression. CLN2 Clinical Rating Scale seizure domain scores indicated a reduction in the frequency of tonic-clonic seizures in treated patients, whereas an increase in frequency was observed in historical controls, suggesting that treatment may also have some benefit on seizures. Consistent with this, the proportion of participants with convulsions AEs declined over time. However, it should be noted that changes in use of antiepileptic drugs, concurrent illnesses, and brain atrophy over disease progression may also affect seizure frequency and severity.

Patients with CLN2 disease suffer from progressive loss of vision and are typically blind by the age of 7-10 years.[11] ICV administration of cerliponase alfa is not expected to have an impact on the retina, and decline in vision accompanied by progressive retinal degradation has been documented in patients receiving treatment.[16] Consistent with this, scores on the vision domain of the CLN2 Clinical Rating Scale were seen to decline in both treated and historical control patients, although the decline was somewhat delayed in treated patients, suggesting that despite the lack of effect on retinal degradation, there may be an impact of treatment on the occipital visual cortex. Studies in canine models of CLN2 disease have demonstrated that intravitreal injection of cerliponase alfa can preserve retinal structure and function[17,18] and clinical trials evaluating the impact of intravitreal cerliponase alfa are ongoing (NCT05152914).

Among treated patients, total gray matter volume declined over the duration of the study. However, most of this decline occurred over the first 49 weeks of treatment, with a smaller incremental loss by week 97, after which little further change was observed. This may suggest that there is an initial loss of cortical gray matter followed by stabilization. Interpretation of these findings is limited by the lack of comparator data for historical untreated controls. However, Loebel et al. have shown progressive loss of supratentorial cortical gray matter (up to 12·5 % per year) in a longitudinal cohort of untreated CLN2 disease patients.[13]

Time to death was evaluated as an exploratory outcome in the study. Median age of death for historical untreated controls was 10·4 years; none of the treated patients died during the study. In CLN2 disease, symptomatic care (e.g., mechanical ventilation, gastrostomy tube feeding) may prolong life, but such measures do not generally alter disease progression and thus prolongation of life may be predominantly in the most progressed stages of disease. Supportive analyses of the primary efficacy endpoint demonstrating a delay in time to reach a score of zero suggest that the increased survival observed in patients treated with cerliponase alfa is accompanied by preservation of function. Assessments of quality of life and achievement of developmental milestones were also considered as exploratory efficacy endpoints in the study. Quality of life scores showed a substantial impairment at study baseline, reflecting the burden of disease and extent of progression in these patients at the time of enrollment. Scores in PedsQL domains relating to physical, social and school functioning were lower at end of study compared to baseline, while the others were minimally changed or higher. Interpretation of the significance of these changes is limited by the lack of comparator data from historical controls as well as the lack of defined, population-specific clinically important difference estimates. Moreover, the high degree of variability seen suggests the need to evaluate these outcomes at the patient level and in the context of disease progression and intercurrent events.

The safety profile of ICV cerliponase alfa was similar to that observed after 96 weeks. The most common SAEs reflect treatment with an exogenous protein and complications arising from use of the ICV device. All participants who experienced Grade 3 hypersensitivity reactions tested negative for the presence of drug-specific IgE antibodies, a hallmark of acute type I hypersensitivity reactions.[19-21] The impact of immunogenicity on safety and efficacy was consistent with previously reported findings based on up to 129 weeks of treatment.[9]

All participants who experienced ICV device-related infections, or who required replacement of the device for other reasons, continued therapy after removal of the device, intravenous antibiotic treatment when appropriate, and subsequent device replacement. The occurrence of device-related infections emphasizes the importance of strict adherence to sterile technique at all times when preparing and administering cerliponase alfa.[22,23] In addition to ICV device replacement following infections or complications, replacement is recommended prior to 4 years of use due to the potential for material degradation.[24] Participants in this study had received treatment for approximately 5 years by its conclusion and more than half were observed to have had a prophylactic device replacement.

The major limitation of both the primary and extension studies is its open-label, non-randomized design and lack of a contemporaneous control group. The natural history cohort had less frequent assessments and a substantially longer epoch of assessment than the treatment group. Bias could arise if changing standard of care had an impact on motor-language assessment in the control group. We note, however, that the natural history database is the largest available and that the duration of follow-up for both natural history patients and treated patients was substantial. To limit the likelihood that findings were the result of bias, a number of supportive analyses were conducted, including patient-level matching and covariate adjustments. All such analyses confirmed the observed treatment benefit, however the potential for unmeasured confounding cannot be excluded. Additionally, for analyses of survival and time to loss of function (motor-language score 0) where few events were observed in treated patients, length of follow-up time is a limitation and although penalization methods were used for analyses, sparse-data bias may remain.[25] The motor-language score itself has inherent limitations in that it does not capture many important aspects of CLN2 disease and, moreover, lacks granularity with domain scores covering a comparatively wide range of abilities. However, it was selected as the primary efficacy outcome in this study because it provided an objective assessment that could be used to compare outcomes in treated patients with those of historical controls.

In conclusion, data from this study demonstrate that long-term ICV administration of cerliponase alfa in children with CLN2 disease slows decline in critical motor and language function compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these were manageable and did not result in treatment discontinuation. A further study in an expanded cohort including children younger than 3 years of age (NCT02678689) will explore outcomes following initiation of cerliponase alfa treatment in presymptomatic children.[26]

Contributions

All authors made substantial contributions to the acquisition and interpretation of study data; revised the manuscript critically for important intellectual content; approved the final version to be published; and are accountable for all aspects of the work. PS conducted the data analyses with consultation from JCP. All the authors vouch for the accuracy and completeness of the

study results, adherence to the protocol, and reporting of AEs. The corresponding author (AS) and sponsor authors (JCP, PS, SB, ACherukuri) directly accessed and verified the study data. All authors had full access, if requested, to all the data in the study and accept responsibility to submit for publication. The manuscript was drafted by a medical writer (Abigail Hunt, an employee of BioMarin) under the direction of the authors.

Declaration of interests

AS and MN have received payments to their institution as a study site according to clinical trial budget, medical writing support, honoraria and travel support from BioMarin Pharmaceutical Inc; EDLR has received salary support as the primary investigator and salary support for the research personnel, honoraria and travel support from BioMarin Pharmaceutical Inc and consulting fees from Zogenix; NS has received consulting fees from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB, Takeda, and Angeun; honoraria from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB and Zogenix; and travel fees BioMarin Pharmaceutical Inc and Jazz Pharma; PG has received payments to his institution as a study site according to clinical trial budget, honoraria and travel support from BioMarin Pharmaceutical Inc; MT has received honoraria from BioMarin Pharmaceutical Inc; SCA has received research salary support from BioMarin Pharmaceutical Inc, research effort support for study on erenumab from Amgen, research effort support for study on Rimegepant from Pfizer, grant support for fellowship training from NINDS/Neuronext and honoraria as associate editor from Pediatric Neurology; DJB and JPD have received contractor fees paid by BioMarin Pharmaceutical Inc for analyzing imaging data that appears in the paper; PS is an employee and stockholder of BioMarin Pharmaceutical Inc; SB and ACherukuri are employees of BioMarin Pharmaceutical Inc; JLCP is an employee & stockholder of BioMarin Pharmaceutical Inc and a scientific advisor for NPKUA; AChakrapani, CS, EW, and LMW reported no conflicts of interest.

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Data sharing

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes.

Additional supporting documents may be available upon request.

Investigators will be able to request access to these data and supporting documents via a data sharing portal beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of relevant product.

Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology.

Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com/patients/publication-data-request/ to determine whether access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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Figure Legends

Figure 1: CLN2 Clinical Rating Scale Outcomes
Panels A and B show Kaplan-Meier curves for time to unreversed 2-point decline from baseline or a score of 0 (Panel A), and time to unreversed score of 0 (Panel B) in the combined score for motor and language domains. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Panels C and D show change from baseline in the score for motor and language function (Panel C) and in the score for all four domains of the CLN2 Rating Scale (motor, language, vision, and seizure domains; Panel D) for treated patients and historical controls. Error bars indicate 95% confidence intervals.

Figure 2: Change from Baseline in Total Gray Matter Volume among Treated Patients
Graph shows the percent change from baseline in total gray matter volume among treated patients. Error bars represent 95% confidence intervals. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Numbers shown on the figure represent the number of patients with available data at each time point.

References

1. Chang M, Cooper JD, Davidson BL, et al. CLN2. In: Mole SE, Williams Re, Goebel HH, eds. The Neuronal Ceroid Lipofuscinoses (Batten Disease). 2nd ed; 2011: 80-109.
2. Sleat DE, Gin RM, Sohar I, et al. Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. *Am J Hum Genet* 1999; **64**(6): 1511-23.
3. Fietz M, AlSayed M, Burke D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. *Mol Genet Metab* 2016; **119**(1-2): 160-7.
4. Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. *Lancet Child Adolesc Health* 2018; **2**(8): 582-90.
5. Kohlschutter A, Schulz A. CLN2 Disease (Classic Late Infantile Neuronal Ceroid Lipofuscinosis). *Pediatr Endocrinol Rev* 2016; **13 Suppl 1**: 682-8.
6. Schulz A, Kohlschutter A, Mink J, Simonati A, Williams R. NCL diseases - clinical perspectives. *Biochim Biophys Acta* 2013; **1832**(11): 1801-6.
7. Schulz A, Ajayi T, Specchio N, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. *N Engl J Med* 2018; **378**(20): 1898-907.
8. Schulz A, Simonati A, Laine M, Williams R, Kohlschutter A, Nickel M. The DEM-CHILD NCL Patient Database: A tool for the evaluation of therapies in neuronal ceroid lipofuscinoses (NCL). *European Journal of Pediatric Neurology* 2015; **19**: S16.
9. Cherukuri A, Cahan H, de Hart G, et al. Immunogenicity to cerliponase alfa intracerebroventricular enzyme replacement therapy for CLN2 disease: Results from a Phase 1/2 study. *Clin Immunol* 2018; **197**: 68-76.
10. Wyrwich KW, Schulz A, Nickel M, et al. An adapted clinical measurement tool for the key symptoms of CLN2 disease. *Journal of Inborn Errors of Metabolism and Screening* 2018; **6**: 1-7.
11. Steinfeld R, Heim P, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. *Am J Med Genet* 2002; **112**(4): 347-54.
12. Worgall S, Kekatpure MV, Heier L, et al. Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. *Neurology* 2007; **69**(6): 521-35.
13. Lobel U, Sedlacik J, Nickel M, et al. Volumetric Description of Brain Atrophy in Neuronal Ceroid Lipofuscinosis 2: Supratentorial Gray Matter Shows Uniform Disease Progression. *AJNR Am J Neuroradiol* 2016; **37**(10): 1938-43.
14. Ru Y, Corado C, Soon RK, Jr., et al. Neurofilament light is a treatment-responsive biomarker in CLN2 disease. *Ann Clin Transl Neurol* 2019; **6**(12): 2437-47.
15. Mole SE, Schulz A, Badoe E, et al. Guidelines on the diagnosis, clinical assessments, treatment and management for CLN2 disease patients. *Orphanet J Rare Dis* 2021; **16**(1): 185.
16. Dulz S, Schwering C, Wildner J, et al. Ongoing retinal degeneration despite intraventricular enzyme replacement therapy with cerliponase alfa in late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2 disease). *Br J Ophthalmol* 2022.
17. Whiting REH, Pearce JW, Vansteenkiste DP, et al. Intravitreal enzyme replacement preserves retinal structure and function in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **197**: 108130.

18. Whiting REH, Robinson Kick G, Ota-Kuroki J, et al. Intravitreal enzyme replacement inhibits progression of retinal degeneration in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **198**: 108135.
19. de Las Vecillas Sanchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug Hypersensitivity and Desensitizations: Mechanisms and New Approaches. *Int J Mol Sci* 2017; **18**(6).
20. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. *Am Fam Physician* 2003; **68**(9): 1781-90.
21. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011; **127**(3 Suppl): S67-73.
22. de Los Reyes E, Lehwald L, Augustine EF, et al. Intracerebroventricular Cerliponase Alfa for Neuronal Ceroid Lipofuscinosis Type 2 Disease: Clinical Practice Considerations From US Clinics. *Pediatr Neurol* 2020; **110**: 64-70.
23. Schwering C, Kammler G, Wibbeler E, et al. Development of the "Hamburg Best Practice Guidelines for ICV-Enzyme Replacement therapy (ERT) in CLN2 Disease" Based on 6 Years Treatment Experience in 48 Patients. *J Child Neurol* 2021; **36**(8): 635-41.
24. Inc. BP. Prescribing Information: BRINEURA (cerliponase alfa) injection, for intraventricular use. 2020.
25. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016; **352**: i1981.
26. Schulz A, de Los Reyes E, Specchio N, et al. Cerliponase alfa for the treatment of CLN2 disease in an expanded patient cohort including children younger than three years: Interim results from an ongoing clinical study. *Mol Genet Metab* 2021; **132**(2): S95.

Table 1. Demographic and Clinical Characteristics of Participants at Baseline (Safety Population)*

	Participants (n=24)
Age at enrollment, years	
Mean (SD)	4·9 (1·28)
Median (IQR)	4·6 (4.0, 5.5)
Range	3·1, 8·9
Sex, n (%)	
Male	9 (38)
Female	15 (63)
Race, n (%)	
Asian	1 (4)
Black	0
White	23 (96)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	1 (4)
Not Hispanic or Latino	23 (96)
Baseline motor/language CLN2 Rating Scale score†	
Mean (SD)	3·5 (1·2)
Median (IQR)	3·0 (3.0, 4.0)
Score, n (%)	
6	2 (8)
5	2 (8)
4	6 (25)
3	11 (46)
2	2 (8)
1	1 (4)
Genotype, n (%)	
2 common alleles‡	9 (38)
1 common and 1 uncommon allele§	8 (33)
2 uncommon alleles	7 (29)

* Percentages may not sum to 100 as a result of rounding
† Score was assessed just prior to first 300 mg dose; higher scores represent higher functioning
‡ Common alleles are c.622C>T and c.509-1G>C
§ Uncommon alleles were c.1448G>A, c.380G>A, c.833A>G, c.1015C>T, c.731T>C, c230-13T>A c.1261T>A, and c.1087delinsTT

SD, standard deviation; IQR, interquartile range

Table 2: Adverse Events: Safety Population

	Participants (n=24)
Common adverse events, n (%)	
Upper respiratory tract infection	21 (88)
Pyrexia	20 (83)
Viral upper respiratory tract infection	19 (79)
Vomiting	19 (79)
Generalized tonic-clonic seizure	16 (67)
Seizure	14 (58)
Constipation	13 (54)
Device end of service	13 (54)
Dysphagia	13 (54)
Epilepsy	13 (54)
Rhinitis	13 (54)
Gait disturbance	12 (50)
Cough	11 (46)
Dystonia	11 (46)
Tremor	11 (46)
Visual impairmemt	11 (46)
Hypersensitivity	10 (42)
Myoclonus	10 (42)
Device-related infection	9 (38)
Diarrhoea	9 (38)
Extensor plantar response	9 (38)
Gastroenteritis	9 (38)
Needle issue	9 (38)
Sleep disorder	9 (38)
Viral infection	9 (38)
Serious adverse events, n (%)	
Any serious adverse event	21 (88)
Device end of service	13 (54)
Hypersensitivity	7 (29)
Device-related infection	7 (29)
Upper respiratory tract infection	5 (21)
Dysphagia	4 (17)
Gastroenteritis	4 (17)
Pleocytosis	3 (13)
Dental caries	2 (8)
Device deployment issue*	2 (8)
Epilepsy	2 (8)
Pharyngitis bacterial	2 (8)
Pyelonephritis	2 (8)
Pyrexia	2 (8)

Common adverse events shown are those reported in more than 35% of the participants.
Serious adverse events shown are those reported in more than 1 participant.
*Device deployment issues included procedural issues during the placement or positioning of the intracerebroventricular device.

Figure 1

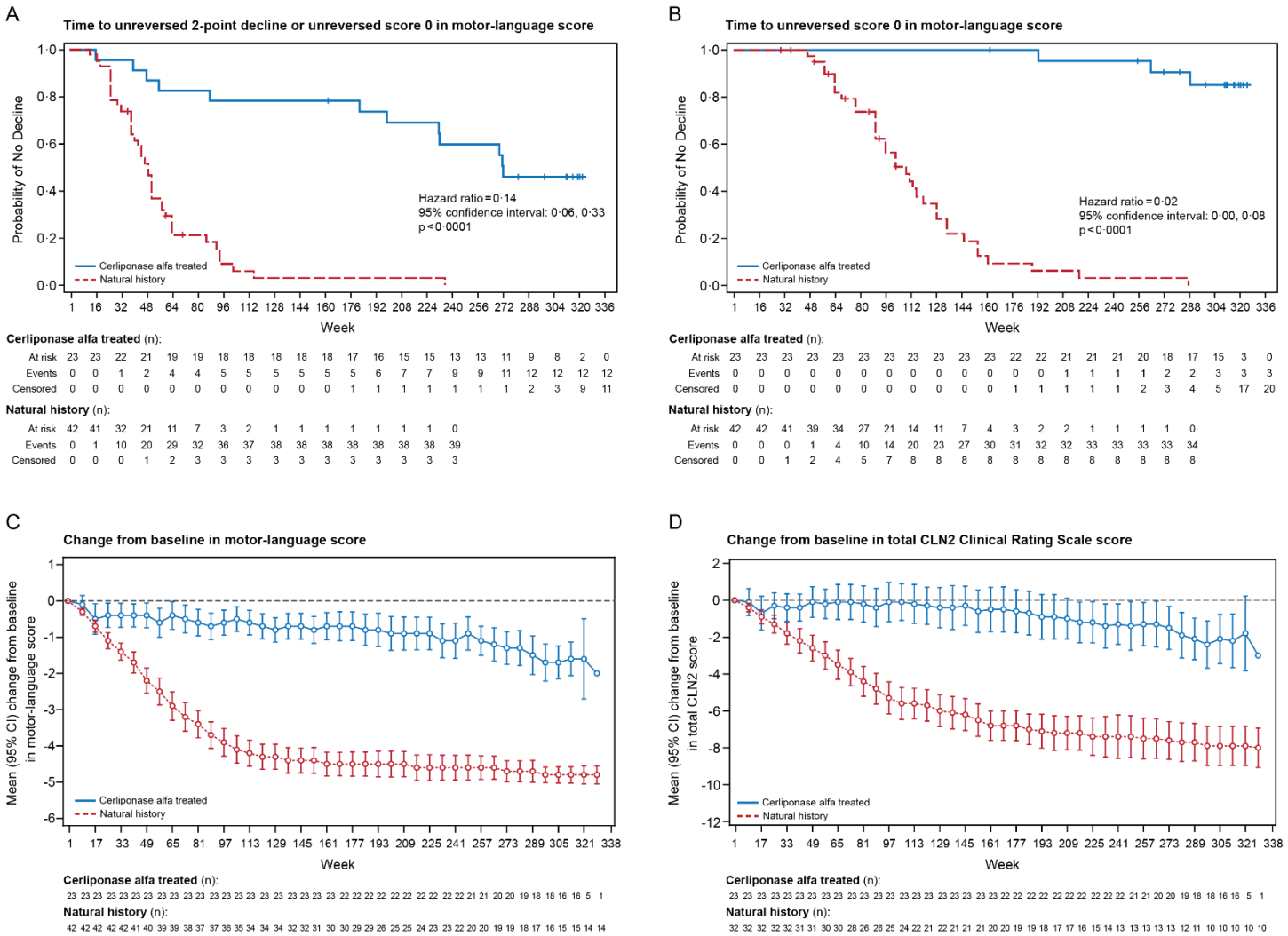
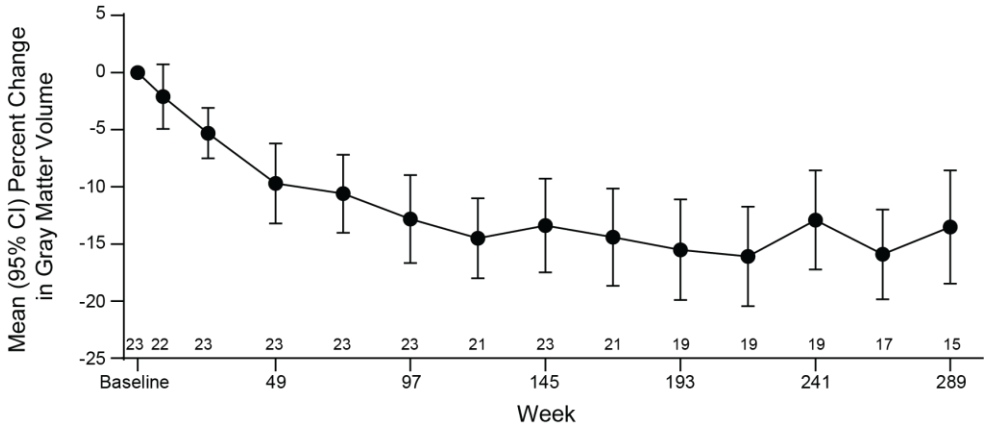

A
Time to unreversed 2-point decline or unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·14
95% confidence interval: 0·06, 0·33
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 22 21 19 19 18 18 18 18 18 17 16 15 15 13 13 11 9 8 2 0
Events 0 0 1 2 4 4 5 5 5 5 5 5 6 7 7 9 9 11 12 12 12 12
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 2 3 9 11
Natural history (n):
At risk 42 41 32 21 11 7 3 2 1 1 1 1 1 1 1 0
Events 0 1 10 20 29 32 36 37 38 38 38 38 38 38 38 39
Censored 0 0 0 1 2 3 3 3 3 3 3 3 3 3 3 3
B
Time to unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·02
95% confidence interval: 0·00, 0·08
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 23 23 23 23 23 23 23 23 23 22 22 21 21 21 20 18 17 15 3 0
Events 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 2 2 3 3 3
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 2 3 4 5 17 20
Natural history (n):
At risk 42 42 41 39 34 27 21 14 11 7 4 3 2 2 1 1 1 1 0
Events 0 0 0 1 4 10 14 20 23 27 30 31 32 32 33 33 33 33 34
Censored 0 0 1 2 4 5 7 8 8 8 8 8 8 8 8 8 8 8 8
C
Change from baseline in motor-language score
Mean (95% CI) change from baseline in motor-language score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 18 18 16 16 5 1
Natural history (n):
42 42 42 42 42 41 40 39 39 38 37 37 36 35 34 34 34 32 32 31 30 30 29 29 26 25 25 24 23 23 22 20 20 19 19 18 17 16 15 15 14 14
D
Change from baseline in total CLN2 Clinical Rating Scale score
Mean (95% CI) change from baseline in total CLN2 score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 19 18 18 16 16 5 1
Natural history (n):
32 32 32 32 32 31 31 30 30 30 28 26 26 25 24 22 21 22 21 21 21 20 20 19 19 18 17 17 16 15 14 13 13 13 13 13 12 11 10 10 10 10 10

Figure 2



Gray Matter Volume	Baseline	49 weeks	97 weeks	145 weeks	193 weeks	241 weeks	289 weeks
Mean (SD) volume, cm^3	452·0 (87·7)	408·3 (88·5)	394·6 (89·3)	390·3 (84·3)	374·2 (89·9)	390·4 (78·4)	371·9 (54·6)
Mean % change from Baseline	-	-10%	-13%	-13%	-16%	-13%	-14%
Annualized % change from Baseline	-	-11%	-14%	-15%	-17%	-14%	-15%
Annualized interval % change	-	-11%	-4%	-1%	-3%	+2%	+1%

Long-Term Open-Label Extension Study of Cerliponase Alfa in Children with CLN2 Disease: Safety and Efficacy After >5 Years of Therapy

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ABSTRACT

BACKGROUND: Cerliponase alfa is a recombinant human tripeptidyl peptidase 1 (TPP1) enzyme replacement therapy for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) caused by mutations in the *TPP1* gene. The aim of this study was to determine the long-term safety and efficacy of intracerebroventricular (ICV) cerliponase alfa in children with CLN2 disease.

METHODS: This analysis includes cumulative data from a 48-week primary study (NCT01907087) and a completed 240-week open-label extension with 6-month safety follow-up (NCT02485899), conducted at 5 hospitals in Germany, Italy, the UK, and the USA between 13 September 2013 and 10 December 2020. Children aged 3-16 years with CLN2 disease confirmed by genetic analysis and enzyme testing were eligible for inclusion. Historical untreated controls with CLN2 disease in the DEM-CHILD database were used as a comparator group. Treatment was ICV infusion of 300 mg cerliponase alfa every 2 weeks. The primary efficacy outcome was time to an unreversed 2-point decline or score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale.

FINDINGS: Twenty-four participants were enrolled in the primary study (15 female, 9 male); 23 participants enrolled in the extension and received 300 mg cerliponase alfa for a mean (range) of 272·1 (162·1–300·1) weeks: 17 participants completed the extension and 7 discontinued prematurely. Treated patients were significantly less likely than historical untreated controls to have an unreversed 2-point decline or score of 0 in the combined motor-language domains (hazard ratio, 0·14; 95% confidence interval, 0·06 to 0·33; $p<0·0001$). All participants experienced ≥1 adverse event (AE) and 21 (88%) experienced a serious AE; 9 participants experienced ICV device-related infections with 9 events in 6 participants resulting in device replacement. There were no study discontinuations because of an AE. There were no deaths and treated patients were significantly less likely to die than historical controls.

INTERPRETATION: Cerliponase alfa treatment over a period of >5 years was seen to confer a clinically meaningful slowing of motor and language function decline in children with CLN2 disease. Although our study is limited by the lack of a contemporaneous control group, the results provide critical insights into the outcomes of long-term treatment.

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RESEARCH IN CONTEXT

Evidence before this study

We conducted a PubMed search for clinical trials published between 1 January 1966 and 24 May 2023, using the text word search terms "CLN2 disease," "neuronal ceroid lipofuscinosis type 2," or "Batten disease", and "cerliponase alfa" without language restriction. To date, the safety, efficacy, and immunogenicity of cerliponase alfa have been assessed in a completed multicentre, single-arm, dose-escalation clinical study (NCT01907087, EudraCT 2012-005430-11) after all participants had received at least 48 weeks of 300 mg dosing and an interim analysis (an additional 48 weeks of data) of a 240-week extension study (NCT02485899, EudraCT 2014-003480-37). Compared with historical controls, patients treated with the recommended 300 mg cerliponase alfa every 2 weeks for at least 96 weeks experienced a statistically significant slowing of decline in motor and language function. Adverse events, including seizures, pyrexia, vomiting, device-related infections, and hypersensitivity reactions, were shown to be manageable and did not result in treatment discontinuation. These data represent a clinically meaningful preservation of motor and language function and an acceptable risk profile and have increasingly led to cerliponase alfa becoming the standard of care for children with CLN2 disease, where this treatment is available.

Added value of this study

This report presents final long-term outcomes (>5 years of treatment) based on cumulative data from the primary and extension studies of safety and efficacy of cerliponase alfa in children with CLN2 disease. Participants in the study ranged in age between 3.1 and 8.9 years at the time of enrolment. After >5 years of follow-up in the long-term extension study, all patients had reached the age at which disease progression would be expected to be very advanced, and thus the data presented here provide additional information about the efficacy of treatment through the expected phase of most rapid decline. Moreover, many patients had reached an age exceeding the typical life expectancy for untreated patients, and a significant impact of treatment on mortality was observed.

Implications of all the available evidence

Taken together, the data show that long-term intracerebroventricular administration of 300 mg cerliponase alfa every 2 weeks in children with CLN2 disease slows decline in critical motor and language functions compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these did not result in treatment discontinuation, and immunogenicity does not appear to be a limiting factor with respect to either safety or efficacy.

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) is a rare, rapidly progressive paediatric neurodegenerative disease caused by mutations in the tripeptidyl peptidase 1 *TPP1* gene resulting in TPP1 enzyme deficiency.[1,2] Deficient activity of TPP1 is associated with intracellular accumulation of lysosomal storage materials and neuronal cell death.[1] Children with CLN2 disease appear healthy at birth and often show delayed language acquisition before other symptoms manifest, typically at age 2-4 years with seizures and ataxia.[1,3,4] The classic late-infantile disease phenotype is characterized by loss of motor and language functions beginning at around 3 years of age and includes language regression and eventual complete loss of expressive language; new onset or worsening ataxia and complex movement disorders resulting in complete loss of independent mobility; worsening epilepsy, which may become intractable; progressive loss of ability to swallow; progressive dementia; deterioration of vision leading to blindness; and death by adolescence.[1,5,6]

In 2017, the European Medicines Agency and the United States Food and Drug Administration approved cerliponase alfa (Brineura; BioMarin Pharmaceutical Inc., Novato, CA) enzyme replacement therapy for treatment of CLN2 disease. Efficacy of cerliponase alfa was demonstrated by comparing changes in the combined motor and language domains of the CLN2 Clinical Rating Scale in treated patients with those in untreated historical controls enrolled in the DEM-CHILD NCL database.[7] Motor and language function are hallmarks of CLN2 disease severity and can be reliably measured by clinical raters: each domain of the CLN2 Clinical Rating Scale is scored from 0 to 3, with a score of 3 representing normal function and a score of 0 representing complete loss of function (Table S1). Compared with untreated historical controls, patients treated with 300 mg of cerliponase alfa for at least 96 weeks were shown to be less likely to experience an unreversed 2-point decline or score of 0 in the combined motor and language domains (hazard ratio [HR], 0·08; 95% confidence interval [CI], 0·02 to 0·23; $p<0·0001$) and had a lower mean rate of decline in motor and language function.[7] Common adverse events (AEs) in treated patients included seizures, pyrexia, vomiting, and hypersensitivity reactions.

We present cumulative data from the primary and completed open-label extension studies to assess the safety and efficacy of cerliponase alfa in children with CLN2 disease over >5 years of treatment.

METHODS

Study Design

Study 190-201 was a 48-week, single-arm, open-label, multicentre, dose-escalation study of intracerebroventricular (ICV) cerliponase alfa, conducted between September 2013 and November 2015 at 5 tertiary care hospitals (1 each in Germany, Italy, and the United States; and 2 in the United Kingdom).[7] Upon completion of the 48-week primary study, participants with a combined motor-language score of >0 on the CLN2 Clinical Rating Scale (Table S1) were eligible to enroll in study 190-202, an open-label extension study conducted between 02 February 2015 and 10 December 2020. Participants continued to receive 300 mg of ICV cerliponase alfa every 2 weeks for 240 weeks (Figure S1). A safety follow-up visit was performed 6 months after completion of the 240-week dosing period. Cumulative data from both the primary and extension studies are presented.

The primary and extension studies were registered at clinicaltrials.gov (NCT01907087 and NCT02485899) and EudraCT (2012-005430-11 and 2014-003480-37). See the Supplementary Material for the extension study protocol and statistical analysis plan.

Participants

Participants eligible to enroll in the primary study were between the ages of 3 and 15 years and had a diagnosis of CLN2 disease confirmed by deficient TPP1 enzyme activity and genetic analysis. Additional inclusion and exclusion criteria can be found in the Supplementary Material.

Written informed consent from a parent or legal guardian of each participant was obtained, and assent was obtained from the participant, if appropriate. The studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by all relevant institutional ethics boards.

The historical control group consisted of CLN2 patients who were enrolled in the DEM-CHILD NCL patient database and who were diagnosed and followed in NCL specialty centers in Hamburg, Germany and Verona, Italy.[4,8]

Procedures

Cerliponase alfa was administered via infusion (at a rate of 2·5 ml/ hour for 4 hours) through an ICV reservoir surgically implanted into the lateral cerebral ventricle. Following the dose-escalation phase of the primary study and during the extension study, participants received 300 mg cerliponase alfa every 2 weeks. Due to the potential for hypersensitivity reactions, prophylactic antihistamine and/or antipyretic could be administered at the investigator's discretion approximately 30 minutes before each infusion. During the extension study, the CLN2 Clinical Rating Scale was administered every 8 weeks. Safety assessments included brief physical exam, AEs, concomitant medication use, vital signs, and cerebrospinal fluid (CSF) surveillance every 2 weeks; clinical laboratory tests, neurologic exam, visual acuity tests, and CSF/serum collection for immunogenicity tests every 12 weeks; and MRI, quality of life assessments, developmental assessments, electrocardiograms, and electroencephalograms every 24 weeks. Complete physical examination was performed every 48 weeks. The attribution of AEs to the study drug or device was determined by the investigator and was not adjudicated. Wherever possible, AEs were recorded with a diagnosis as the AE term rather than as a series of terms relating to a diagnosis.

Validated assays were used to assess serum and CSF anti-drug total antibody (TAb) and CSF neutralizing antibody (NAb) titers.[9] NAb testing was performed on baseline CSF samples and on subsequent CSF samples found to be TAb positive. Drug-specific immunoglobulin E (IgE) testing was performed on serum samples collected in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or hypersensitivity adverse event (HAE) of Grade 3 or higher. See appendix for additional details regarding immunogenicity monitoring methods.

Outcomes

The primary efficacy outcome of study 190-202 was the time to first unreversed 2-point decline or unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale, comparing treated patients with historical untreated controls (see Supplementary Material for details regarding the scale and its assessment).[10-12] An unreversed 2-point decline was defined as a decline that had not returned to within 1 point of baseline score by the last

assessment. The same principal investigator, or a qualified physician designated by the principal investigator, who was continuously trained on the CLN2 Clinical Rating Scale, assessed subjects at their study site.

Pre-specified supportive analyses of the primary efficacy outcome included assessment of time to first unreversed 2-point decline or a score of 0 on the separate motor and language domains of the CLN2 Clinical Rating Scale; time to unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale; rate of decline in the combined motor-language score; and change from baseline in the combined motor-language score, total CLN2 Clinical Rating Scale score (motor, language, vision, seizure domains), and individual domain scores. For each, outcomes in treated patients were compared with historical untreated controls.

The secondary efficacy endpoint was brain atrophy, evaluated by volumetric MRI in treated patients considering one or more of the following: whole brain volume, percent cerebrospinal fluid, percent gray matter, percent white matter, whole brain apparent diffusion coefficient and cortical thickness. Data on whole brain percent gray matter is presented here as it is the most well described in published natural history studies of CLN2 disease patients.[13] Analyses of additional MRI parameters, pooling data from multiple studies, are ongoing and will be reported separately.

Exploratory efficacy endpoints were survival, CSF and plasma biomarkers, developmental milestones (Denver II Development Scale), anti-epileptic treatment, Quality of Life (Pediatric Quality of Life Inventory [PedsQL] Parent Report for Toddlers and Parent Family Impact; CLN2 disease-based Quality of Life), retinal anatomy using optical coherence tomography, visual acuity, and electroencephalograms. Analyses of survival, quality of life, and developmental milestone data are presented in the Supplementary Materials. Data collected on CSF and plasma biomarkers, anti-epileptic treatment, retinal anatomy, visual acuity, and electroencephalograms are not reported here. Retinal anatomy and visual acuity assessments were only conducted in the extension study and were added as part of a protocol amendment, limiting their utility for evaluating progression of retinal disease due to lack of baseline and data over the first year of treatment. Data on neurofilament light (NF-L) as a potential biomarker for CLN2 disease collected in the primary and extension studies have been published elsewhere.[14] Data on other outcomes are the subject of ongoing analyses.

Statistical Analysis

No formal sample size calculations were performed: sample size for the primary study was based on the ultra-rare nature of CLN2 disease.

All participants who received more than 1 dose of cerliponase alfa were included in efficacy analyses and were compared with evaluable untreated historical controls enrolled in the DEM-CHILD NCL registry.[4,8] Baseline measurement for treated patients was defined as the last observation preceding the first administration of a 300 mg dose of cerliponase alfa. For patients in the historical control cohort, baseline score on the combined motor-language scale was defined as the first score of less than 6 occurring at the age of 36 months or more; the age at baseline assessment was calculated as the midpoint of the age range of assessments at the time this score was obtained.

Kaplan-Meier methods and the Cox proportional-hazards model were used to compare the time to unreversed 2-point decline or a score of 0 and the time to unreversed score of 0 on the

combined motor-language domains for treated patients and historical controls. Follow-up was from baseline to time of unreversed 2-point decline or score zero (event) or time of last CLN2 clinical rating scale assessment (censoring). The Cox model included baseline combined motor-language score, age, genotype (common alleles), and sex as covariates. Similar analyses were performed to examine differences in the motor and language domain scores alone, as well as time to score of 0 on the combined motor-language domains.

Rate of decline in the combined motor-language score was calculated as the change from baseline to last assessment with a score of more than 0 divided by the length of follow-up and compared between treated patients and historical controls using a 2-sample t-test based on unequal variances. Change from baseline in the CLN2 Clinical Rating Scale score was calculated for 2 domains (motor and language; range 0-6), 4 domains (motor, language, vision, and seizures; range, 0-12), and for individual domains (for each, range 0-3) and compared between treated patients and historical controls. Confirmatory analyses of change from baseline were also performed in matched cohorts (see Supplementary Methods).

Changes in brain volume for treated patients, assessed by non-contrast whole brain MRI, were summarized by timepoint as absolute and percent changes from baseline.

Methods used for analyses of exploratory efficacy endpoints (mortality, quality of life, and developmental milestones) are described in the Supplementary Materials.

Safety data presented include all AEs reported in the primary and extension studies from the last observation preceding device implantation until 6 months after either the last administration of study drug or early termination visit. Relationships between immunogenicity and safety or efficacy endpoints were explored for TAb-negative and TAb-positive patients using box-plots. Seizure AEs mapping to the Convulsions Standardized MedDRA Query (SMQ) were assessed for consecutive 24-week intervals.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Role of the Funding Source

The study was funded by BioMarin Pharmaceutical, Inc. The funder designed the study with input from the investigators and health authorities, and provided the study medication. Data were collected by the investigators and were entered into an electronic data capture system maintained by the funder. Data were analyzed by the funder according to a prespecified statistical analysis plan agreed upon with the study investigators; interpretation of the study data was performed by the funder in conjunction with the investigators. Authors employed by the funder (JCP, PS, SB, ACherukuri) contributed to the development of the manuscript in conjunction with the other authors. Assistance with manuscript preparation was provided by a medical writer employed by the funder.

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RESULTS

Participants were screened and enrolled in the primary study between 13 September 2013 and 22 December 2014. All 24 participants who enrolled in the primary study were evaluated for safety. One participant withdrew from the primary study at the parents' request after receiving 1

dose of the study drug due to an inability to comply with study procedures, and was excluded from efficacy analyses. Incidence rates for AEs may therefore be slightly under-reported due to the very early termination of 1 participant. Of the 23 participants who received more than 1 dose of cerliponase alfa, all completed the primary study and enrolled in the extension study. Seventeen of the 23 participants who enrolled in the extension study completed the planned follow-up. Six participants withdrew from the extension study: 4 due to relocation or switch to commercial therapy and 2 due to meeting study stopping criteria, having a score of 0 in the combined motor-language domains assessed at consecutive study visits. For participants who withdrew, all data up until the last available assessment were included for analysis. The database of untreated historical controls contained 69 individuals of whom 42 satisfied the criteria for comparability to the treated population.

Demographic and clinical characteristics of enrolled participants are summarized in Table 1. The population included 9 males (37.5%) and 15 (62.5%) females. The mean (SD) age at the time of enrollment in the primary study was 4·9 (1·3) years and the mean (SD) score on the combined motor-language domains of the CLN2 Clinical Rating Scale at 300 mg baseline was 3·5 (1·2), (range, 1 to 6). The safety population (n=24) was followed for a mean (SD) treatment duration of 263·2 (67·9) weeks (range, 0·1 to 309·1). The 23 participants who enrolled in the extension study and were evaluated for efficacy received 300 mg of cerliponase alfa for a mean (SD) of 272·1 (37·4) weeks (range, 162·1–300·1). A total of 3142 infusions were administered across both studies, with 3113 infusions at the 300 mg dose; the mean (SD) number of infusions per participant at any dose was 130·9 (33·5).

Treated patients were significantly less likely than historical controls to have an unreversed 2-point decline or a score of 0 in the combined motor-language domains (Figure 1A; HR, 0·14; 95% CI, 0·06 to 0·33; $p<0·0001$). The median (95% CI) time to event was 272 weeks (lower CI, 199 weeks; upper CI not estimable) in treated patients compared to 49 weeks (95% CI, 39 to 58) in historical controls. Similar results were observed for the motor and language domains individually (Figure S2A and S2B, respectively). Treated patients were also significantly less likely than historical controls to reach an unreversed score of 0 in the combined motor-language domains, representing complete loss of ability to ambulate and communicate (Figure 1B; HR, 0·02; 95% CI, 0·00 to 0·08; $p<0·0001$). The median time to reach an unreversed score of 0 was 109 weeks (95% CI, 90 to 129) in historical controls; only 3 treated patients reached an unreversed score of 0 by study completion and the median time to score 0 was not estimable. All 3 patients who reached a score of 0 had a baseline motor-language score of 3: one reached a score of 0 only at the study completion visit (week 288), one patient reached a score of 0 at week 264, and one patient at week 193.

The estimated mean (SD) rate of decline in the combined motor-language score was 0·38 (0·50) points per 48 weeks among treated patients (range: 0·00 to 2·18) and 2·13 (0·95) points per 48 weeks among historical controls (range: 0·45 to 4·27), a mean difference of 1·75 points (95% CI, 1·39 to 2·11; $p<0·0001$). After adjustment for baseline covariates (age, baseline motor-language score, sex, and genotype), the rate of decline was 0·64 (0·09) points per 48 weeks among the treated patients and 1·99 (0·14) points per 48 weeks among historical controls, a mean difference of 1·35 points (95% CI, 0·99 to 1·71; $p<0·0001$).

Combined motor-language score was seen to decline rapidly in the historical controls (Figure 1C), with scores approaching 0 by week 145. Treated patients showed a gradual decline from

baseline over time reaching a mean (SD) score of 2·8 (1·43) points by week 145 and 1·8 [1·07] by week 313. Similarly, a rapid decline in total CLN2 Clinical Rating Scale score (motor, language, vision, and seizure domains) was observed for historical controls compared with a more gradual decline in treated patients (Figure 1D). Similar results were attained in analyses performed in matched cohorts (see supplemental results; Figures S3-S5).

Data on change from baseline in individual CLN2 Clinical Rating Scale domain scores are shown in Figure S6 and Table S2. Vision domain score was seen to decline in both groups, albeit more rapidly in the historical controls (Figure S6). Treated patients showed a mean decline of 1.4 points from baseline to week 289 compared with a decline of 2.3 points for historical controls (Table S2). The seizure domain score provides an assessment of the frequency of tonic-clonic seizures: mean (SD) seizure domain score increased from 1·7 (1·2) at baseline to 2·4 (0·8) at week 289 in treated patients but decreased from 1·7 (1·1) to 0·7 (1·2) in historical controls, indicating declining frequency of seizures in treated patients and increasing frequency of seizures in historical controls (Table S2 and Figure S6).

Mean percentage change from baseline in total gray matter volume of treated patients, assessed by MRI, is shown in Figure 2. The mean absolute change from baseline to week 49 (end of the primary study) was -9·7%. At week 145, the observed change from baseline was -13·4% and, as of the last observation in the study, the change from baseline was -14·7%.

Data on exploratory efficacy endpoints (mortality [Figure S7], quality of life [Tables S3 and S4], and developmental milestones [Table S5]) are presented in the Supplementary Materials.

All participants experienced at least 1 AE (Table 2 and Table S6). Most AEs were Grade 1 or 2 in severity; 18 participants (75%) had at least one AE of Grade 3 and 3 participants (13%) had a Grade 4 AE. Grade 4 AEs were blindness, pyelonephritis, and status epilepticus. Fifteen participants experienced 52 AEs leading to dose interruptions; no AEs led to dose reduction. There were no deaths and no study discontinuations because of an AE. A total of 237 AEs in 23 participants were considered related to study drug; the most common drug-related AEs were pyrexia (127 events in 11 participants), hypersensitivity (16 events in 10 participants), seizure (14 events in 9 participants), vomiting (15 events in 6 participants), and epilepsy (4 events in 4 participants).

Overall, 107 serious adverse events (SAEs) were reported in 21 participants (88%) (Table 2 and Table S7). A total of 12 SAEs in 8 participants were considered related to study drug; the most common drug-related SAEs were hypersensitivity (9 events in 7 participants), infusion-associated reaction (2 events in 1 participant), pleocytosis (1 event in 1 participant).

Eighteen participants (75%) had a total of 56 hypersensitivity AEs (HAEs; Table S8); 29 were Grade 1, 19 were Grade 2, and 8 were Grade 3. There were no AEs of anaphylaxis or anaphylactoid reactions according to the criteria of the US National Institute of Allergy and Infectious Diseases. Twenty-one participants (88%) had a combined 79 device-related AEs (Table S9): the most common were device-related infections (15 events in 9 participants) and device end-of-service events, representing prophylactic replacement of the ICV device (13 events in 13 participants). A total of 29 device-related SAEs were reported in 16 participants, including 12 device-related infections in 7 participants. A total of 14 device-related AEs in 7 participants led to ICV device replacement (2 participants had 3 device replacement; 2 participants had 2 replacements, and 3 participants had a single replacement): device-related infection (9 events in 6 participants), device leakage (2 events in 2 participants), device

deployment issue (2 events in 2 participants), and device malfunction (1 event in 1 participant). Device-related infections were managed with intravenous antibiotics, with the specific agent used being determined based on the organism identified. In all cases, the ICV device was successfully replaced without complication and without discontinuation of study drug.

A total of 7 participants (29%) experienced 15 cardiovascular events (most common were: bradycardia, 4 events; hypotension, 4 events; hematoma, 2 events) and 23 participants (96%) experienced 693 events mapping to the convulsions Standardized MedDRA Query (Table S10). No events of hydrocephalus, meningitis, or unexpected rapid decline in motor-language score were reported. The proportion of participants who reported ≥1 event of convulsions as an AE declined from 88% (n=21) during weeks 0-24, reaching a nadir of 26% (n=23) during weeks >144 to 168, before increasing to 59% (n=13) in weeks >216 (Figure S8).

The anti-drug antibody (ADA) response in all participants by time on treatment is displayed for CSF TAb (Figure S9A) and serum TAb (Figure S9B). CSF TAb response was detected in 10 participants (42%); earliest time to onset was 13 weeks. CSF TAb titers returned to undetectable levels in 9 out of 10 ADA positive participants by the end of the study. Serum TAb response was detected in 19 participants (79%); titers were sustained in 12/19 (63%), declined in 5/19 (26%), and reverted to undetectable in 2/19 (11%) by the end of the study. Low titer NAb were detected in the CSF of 3 participants (13%) at a single visit. Change from baseline in the combined motor-language score was comparable between CSF TAb-negative and TAb-positive participants (Figure S10). Six participants reported 8 Grade 3 HAEs; however, no association was found between serum ADA titer and either the incidence or severity of HAEs (Figure S11A and S11B, respectively). Serum samples collected from all participants reporting Grade 3 HAEs were tested and found negative for drug-specific IgE.

DISCUSSION

Intracerebroventricular cerliponase alfa is the first disease-modifying treatment approved for CLN2 disease. Treatment with 300 mg cerliponase alfa every other week for at least 96 weeks was shown to result in meaningful preservation of motor and language function, with acceptable safety and tolerability,[7] and cerliponase alfa has increasingly become the standard of care for children with CLN2 disease, where available.[15] In this report, we confirm that slowing of clinical disease progression is maintained through >5 years of treatment, with expected but manageable safety events. After completion of the 240-week treatment period of the study, participants were not required to continue on treatment. However, all who completed the treatment period did indeed continue to receive infusions and remained on treatment at the time of the 6-month safety follow-up visit.

After receiving cerliponase alfa for at least 162 weeks at the 300 mg dose, treated patients were found to be less likely than historical untreated controls to experience an unreversed 2-point decline or a score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale. The mean (SD) rate of decline in the combined motor-language domain score was 1·75 points/48 weeks lower for treated patients than for historical controls. Rates of decline were comparable to those reported after 96 weeks of treatment suggesting that attenuation of disease progression is maintained. Although a decline in motor-language score was still seen in treated patients, the attenuation relative to historical controls was clinically meaningful: by the end of study, motor-language score in treated patients had declined by approximately 1.5 points to a median score of 2: at this level children require assistance to walk and have limited language. In

comparison, for historical controls, the median time to reach a motor-language score of 0, representing complete loss of ambulation and ability to communicate through speech, was 109 weeks.

Seizures are a predominant feature of CLN2 disease and remain a significant burden throughout disease progression. CLN2 Clinical Rating Scale seizure domain scores indicated a reduction in the frequency of tonic-clonic seizures in treated patients, whereas an increase in frequency was observed in historical controls, suggesting that treatment may also have some benefit on seizures. Consistent with this, the proportion of participants with convulsions AEs declined over time. However, it should be noted that changes in use of antiepileptic drugs, concurrent illnesses, and brain atrophy over disease progression may also affect seizure frequency and severity.

Patients with CLN2 disease suffer from progressive loss of vision and are typically blind by the age of 7-10 years.[11] ICV administration of cerliponase alfa is not expected to have an impact on the retina, and decline in vision accompanied by progressive retinal degradation has been documented in patients receiving treatment.[16] Consistent with this, scores on the vision domain of the CLN2 Clinical Rating Scale were seen to decline in both treated and historical control patients, although the decline was somewhat delayed in treated patients, suggesting that despite the lack of effect on retinal degradation, there may be an impact of treatment on the occipital visual cortex. Studies in canine models of CLN2 disease have demonstrated that intravitreal injection of cerliponase alfa can preserve retinal structure and function[17,18] and clinical trials evaluating the impact of intravitreal cerliponase alfa are ongoing (NCT05152914).

Among treated patients, total gray matter volume declined over the duration of the study. However, most of this decline occurred over the first 49 weeks of treatment, with a smaller incremental loss by week 97, after which little further change was observed. This may suggest that there is an initial loss of cortical gray matter followed by stabilization. Interpretation of these findings is limited by the lack of comparator data for historical untreated controls. However, Loebel et al. have shown progressive loss of supratentorial cortical gray matter (up to 12·5 % per year) in a longitudinal cohort of untreated CLN2 disease patients.[13]

Time to death was evaluated as an exploratory outcome in the study. Median age of death for historical untreated controls was 10·4 years; none of the treated patients died during the study. In CLN2 disease, symptomatic care (e.g., mechanical ventilation, gastrostomy tube feeding) may prolong life, but such measures do not generally alter disease progression and thus prolongation of life may be predominantly in the most progressed stages of disease. Supportive analyses of the primary efficacy endpoint demonstrating a delay in time to reach a score of zero suggest that the increased survival observed in patients treated with cerliponase alfa is accompanied by preservation of function. Assessments of quality of life and achievement of developmental milestones were also considered as exploratory efficacy endpoints in the study. Quality of life scores showed a substantial impairment at study baseline, reflecting the burden of disease and extent of progression in these patients at the time of enrollment. Scores in PedsQL domains relating to physical, social and school functioning were lower at end of study compared to baseline, while the others were minimally changed or higher. Interpretation of the significance of these changes is limited by the lack of comparator data from historical controls as well as the lack of defined, population-specific clinically important difference estimates. Moreover, the high degree of variability seen suggests the need to evaluate these outcomes at the patient level and in the context of disease progression and intercurrent events.

The safety profile of ICV cerliponase alfa was similar to that observed after 96 weeks. The most common SAEs reflect treatment with an exogenous protein and complications arising from use of the ICV device. All participants who experienced Grade 3 hypersensitivity reactions tested negative for the presence of drug-specific IgE antibodies, a hallmark of acute type I hypersensitivity reactions.[19-21] The impact of immunogenicity on safety and efficacy was consistent with previously reported findings based on up to 129 weeks of treatment.[9]

All participants who experienced ICV device-related infections, or who required replacement of the device for other reasons, continued therapy after removal of the device, intravenous antibiotic treatment when appropriate, and subsequent device replacement. The occurrence of device-related infections emphasizes the importance of strict adherence to sterile technique at all times when preparing and administering cerliponase alfa.[22,23] In addition to ICV device replacement following infections or complications, replacement is recommended prior to 4 years of use due to the potential for material degradation.[24] Participants in this study had received treatment for approximately 5 years by its conclusion and more than half were observed to have had a prophylactic device replacement.

The major limitation of both the primary and extension studies is its open-label, non-randomized design and lack of a contemporaneous control group. The natural history cohort had less frequent assessments and a substantially longer epoch of assessment than the treatment group. Bias could arise if changing standard of care had an impact on motor-language assessment in the control group. We note, however, that the natural history database is the largest available and that the duration of follow-up for both natural history patients and treated patients was substantial. To limit the likelihood that findings were the result of bias, a number of supportive analyses were conducted, including patient-level matching and covariate adjustments. All such analyses confirmed the observed treatment benefit, however the potential for unmeasured confounding cannot be excluded. Additionally, for analyses of survival and time to loss of function (motor-language score 0) where few events were observed in treated patients, length of follow-up time is a limitation and although penalization methods were used for analyses, sparse-data bias may remain.[25] The motor-language score itself has inherent limitations in that it does not capture many important aspects of CLN2 disease and, moreover, lacks granularity with domain scores covering a comparatively wide range of abilities. However, it was selected as the primary efficacy outcome in this study because it provided an objective assessment that could be used to compare outcomes in treated patients with those of historical controls.

In conclusion, data from this study demonstrate that long-term ICV administration of cerliponase alfa in children with CLN2 disease slows decline in critical motor and language function compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these were manageable and did not result in treatment discontinuation. A further study in an expanded cohort including children younger than 3 years of age (NCT02678689) will explore outcomes following initiation of cerliponase alfa treatment in presymptomatic children.[26]

Contributions

All authors made substantial contributions to the acquisition and interpretation of study data; revised the manuscript critically for important intellectual content; approved the final version to be published; and are accountable for all aspects of the work. PS conducted the data analyses with consultation from JCP. All the authors vouch for the accuracy and completeness of the

study results, adherence to the protocol, and reporting of AEs. The corresponding author (AS) and sponsor authors (JCP, PS, SB, ACherukuri) directly accessed and verified the study data. All authors had full access, if requested, to all the data in the study and accept responsibility to submit for publication. The manuscript was drafted by a medical writer (Abigail Hunt, an employee of BioMarin) under the direction of the authors.

Declaration of interests

AS and MN have received payments to their institution as a study site according to clinical trial budget, medical writing support, honoraria and travel support from BioMarin Pharmaceutical Inc; EDLR has received salary support as the primary investigator and salary support for the research personnel, honoraria and travel support from BioMarin Pharmaceutical Inc and consulting fees from Zogenix; NS has received consulting fees from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB, Takeda, and Angeun; honoraria from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB and Zogenix; and travel fees BioMarin Pharmaceutical Inc and Jazz Pharma; PG has received payments to his institution as a study site according to clinical trial budget, honoraria and travel support from BioMarin Pharmaceutical Inc; MT has received honoraria from BioMarin Pharmaceutical Inc; SCA has received research salary support from BioMarin Pharmaceutical Inc, research effort support for study on erenumab from Amgen, research effort support for study on Rimegepant from Pfizer, grant support for fellowship training from NINDS/Neuronext and honoraria as associate editor from Pediatric Neurology; DJB and JPD have received contractor fees paid by BioMarin Pharmaceutical Inc for analyzing imaging data that appears in the paper; PS is an employee and stockholder of BioMarin Pharmaceutical Inc; SB and ACherukuri are employees of BioMarin Pharmaceutical Inc; JLCP is an employee & stockholder of BioMarin Pharmaceutical Inc and a scientific advisor for NPKUA; AChakrapani, CS, EW, and LMW reported no conflicts of interest.

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Data sharing

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes.

Additional supporting documents may be available upon request.

Investigators will be able to request access to these data and supporting documents via a data sharing portal beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of relevant product.

Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology.

Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com/patients/publication-data-request/ to determine whether access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

Acknowledgements

We thank the study patients and their families for their participation and staff members who provided clinical assistance during the course of the study.

Figure Legends

Figure 1: CLN2 Clinical Rating Scale Outcomes
Panels A and B show Kaplan-Meier curves for time to unreversed 2-point decline from baseline or a score of 0 (Panel A), and time to unreversed score of 0 (Panel B) in the combined score for motor and language domains. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Panels C and D show change from baseline in the score for motor and language function (Panel C) and in the score for all four domains of the CLN2 Rating Scale (motor, language, vision, and seizure domains; Panel D) for treated patients and historical controls. Error bars indicate 95% confidence intervals.

Figure 2: Change from Baseline in Total Gray Matter Volume among Treated Patients
Graph shows the percent change from baseline in total gray matter volume among treated patients. Error bars represent 95% confidence intervals. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Numbers shown on the figure represent the number of patients with available data at each time point.

References

1. Chang M, Cooper JD, Davidson BL, et al. CLN2. In: Mole SE, Williams Re, Goebel HH, eds. The Neuronal Ceroid Lipofuscinoses (Batten Disease). 2nd ed; 2011: 80-109.
2. Sleat DE, Gin RM, Sohar I, et al. Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. *Am J Hum Genet* 1999; **64**(6): 1511-23.
3. Fietz M, AlSayed M, Burke D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. *Mol Genet Metab* 2016; **119**(1-2): 160-7.
4. Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. *Lancet Child Adolesc Health* 2018; **2**(8): 582-90.
5. Kohlschutter A, Schulz A. CLN2 Disease (Classic Late Infantile Neuronal Ceroid Lipofuscinosis). *Pediatr Endocrinol Rev* 2016; **13 Suppl 1**: 682-8.
6. Schulz A, Kohlschutter A, Mink J, Simonati A, Williams R. NCL diseases - clinical perspectives. *Biochim Biophys Acta* 2013; **1832**(11): 1801-6.
7. Schulz A, Ajayi T, Specchio N, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. *N Engl J Med* 2018; **378**(20): 1898-907.
8. Schulz A, Simonati A, Laine M, Williams R, Kohlschutter A, Nickel M. The DEM-CHILD NCL Patient Database: A tool for the evaluation of therapies in neuronal ceroid lipofuscinoses (NCL). *European Journal of Pediatric Neurology* 2015; **19**: S16.
9. Cherukuri A, Cahan H, de Hart G, et al. Immunogenicity to cerliponase alfa intracerebroventricular enzyme replacement therapy for CLN2 disease: Results from a Phase 1/2 study. *Clin Immunol* 2018; **197**: 68-76.
10. Wyrwich KW, Schulz A, Nickel M, et al. An adapted clinical measurement tool for the key symptoms of CLN2 disease. *Journal of Inborn Errors of Metabolism and Screening* 2018; **6**: 1-7.
11. Steinfeld R, Heim P, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. *Am J Med Genet* 2002; **112**(4): 347-54.
12. Worgall S, Kekatpure MV, Heier L, et al. Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. *Neurology* 2007; **69**(6): 521-35.
13. Lobel U, Sedlacik J, Nickel M, et al. Volumetric Description of Brain Atrophy in Neuronal Ceroid Lipofuscinosis 2: Supratentorial Gray Matter Shows Uniform Disease Progression. *AJNR Am J Neuroradiol* 2016; **37**(10): 1938-43.
14. Ru Y, Corado C, Soon RK, Jr., et al. Neurofilament light is a treatment-responsive biomarker in CLN2 disease. *Ann Clin Transl Neurol* 2019; **6**(12): 2437-47.
15. Mole SE, Schulz A, Badoe E, et al. Guidelines on the diagnosis, clinical assessments, treatment and management for CLN2 disease patients. *Orphanet J Rare Dis* 2021; **16**(1): 185.
16. Dulz S, Schwering C, Wildner J, et al. Ongoing retinal degeneration despite intraventricular enzyme replacement therapy with cerliponase alfa in late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2 disease). *Br J Ophthalmol* 2022.
17. Whiting REH, Pearce JW, Vansteenkiste DP, et al. Intravitreal enzyme replacement preserves retinal structure and function in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **197**: 108130.

18. Whiting REH, Robinson Kick G, Ota-Kuroki J, et al. Intravitreal enzyme replacement inhibits progression of retinal degeneration in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **198**: 108135.
19. de Las Vecillas Sanchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug Hypersensitivity and Desensitizations: Mechanisms and New Approaches. *Int J Mol Sci* 2017; **18**(6).
20. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. *Am Fam Physician* 2003; **68**(9): 1781-90.
21. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011; **127**(3 Suppl): S67-73.
22. de Los Reyes E, Lehwald L, Augustine EF, et al. Intracerebroventricular Cerliponase Alfa for Neuronal Ceroid Lipofuscinosis Type 2 Disease: Clinical Practice Considerations From US Clinics. *Pediatr Neurol* 2020; **110**: 64-70.
23. Schwering C, Kammler G, Wibbeler E, et al. Development of the "Hamburg Best Practice Guidelines for ICV-Enzyme Replacement therapy (ERT) in CLN2 Disease" Based on 6 Years Treatment Experience in 48 Patients. *J Child Neurol* 2021; **36**(8): 635-41.
24. Inc. BP. Prescribing Information: BRINEURA (cerliponase alfa) injection, for intraventricular use. 2020.
25. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016; **352**: i1981.
26. Schulz A, de Los Reyes E, Specchio N, et al. Cerliponase alfa for the treatment of CLN2 disease in an expanded patient cohort including children younger than three years: Interim results from an ongoing clinical study. *Mol Genet Metab* 2021; **132**(2): S95.

628 **Table 1. Demographic and Clinical Characteristics of Participants at Baseline (Safety Population)***

	Participants (n=24)
Age at enrollment, years	
Mean (SD)	4·9 (1·28)
Median (IQR)	4·6 (4.0, 5.5)
Range	3·1, 8·9
Sex, n (%)	
Male	9 (38)
Female	15 (63)
Race, n (%)	
Asian	1 (4)
Black	0
White	23 (96)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	1 (4)
Not Hispanic or Latino	23 (96)
Baseline motor/language CLN2 Rating Scale score†	
Mean (SD)	3·5 (1·2)
Median (IQR)	3·0 (3.0, 4.0)
Score, n (%)	
6	2 (8)
5	2 (8)
4	6 (25)
3	11 (46)
2	2 (8)
1	1 (4)
Genotype, n (%)	
2 common alleles‡	9 (38)
1 common and 1 uncommon allele§	8 (33)
2 uncommon alleles	7 (29)

* Percentages may not sum to 100 as a result of rounding
† Score was assessed just prior to first 300 mg dose; higher scores represent higher functioning
‡ Common alleles are c.622C>T and c.509-1G>C
§ Uncommon alleles were c.1448G>A, c.380G>A, c.833A>G, c.1015C>T, c.731T>C, c230-13T>A c.1261T>A, and c.1087delinsTT

SD, standard deviation; IQR, interquartile range

629

Table 2: Adverse Events: Safety Population

	Participants (n=24)
Common adverse events, n (%)	
Upper respiratory tract infection	21 (88)
Pyrexia	20 (83)
Viral upper respiratory tract infection	19 (79)
Vomiting	19 (79)
Generalized tonic-clonic seizure	16 (67)
Seizure	14 (58)
Constipation	13 (54)
Device end of service	13 (54)
Dysphagia	13 (54)
Epilepsy	13 (54)
Rhinitis	13 (54)
Gait disturbance	12 (50)
Cough	11 (46)
Dystonia	11 (46)
Tremor	11 (46)
Visual impairmemt	11 (46)
Hypersensitivity	10 (42)
Myoclonus	10 (42)
Device-related infection	9 (38)
Diarrhoea	9 (38)
Extensor plantar response	9 (38)
Gastroenteritis	9 (38)
Needle issue	9 (38)
Sleep disorder	9 (38)
Viral infection	9 (38)
Serious adverse events, n (%)	
Any serious adverse event	21 (88)
Device end of service	13 (54)
Hypersensitivity	7 (29)
Device-related infection	7 (29)
Upper respiratory tract infection	5 (21)
Dysphagia	4 (17)
Gastroenteritis	4 (17)
Pleocytosis	3 (13)
Dental caries	2 (8)
Device deployment issue*	2 (8)
Epilepsy	2 (8)
Pharyngitis bacterial	2 (8)
Pyelonephritis	2 (8)
Pyrexia	2 (8)

Common adverse events shown are those reported in more than 35% of the participants.
Serious adverse events shown are those reported in more than 1 participant.
*Device deployment issues included procedural issues during the placement or positioning of the intracerebroventricular device.

Figure 1

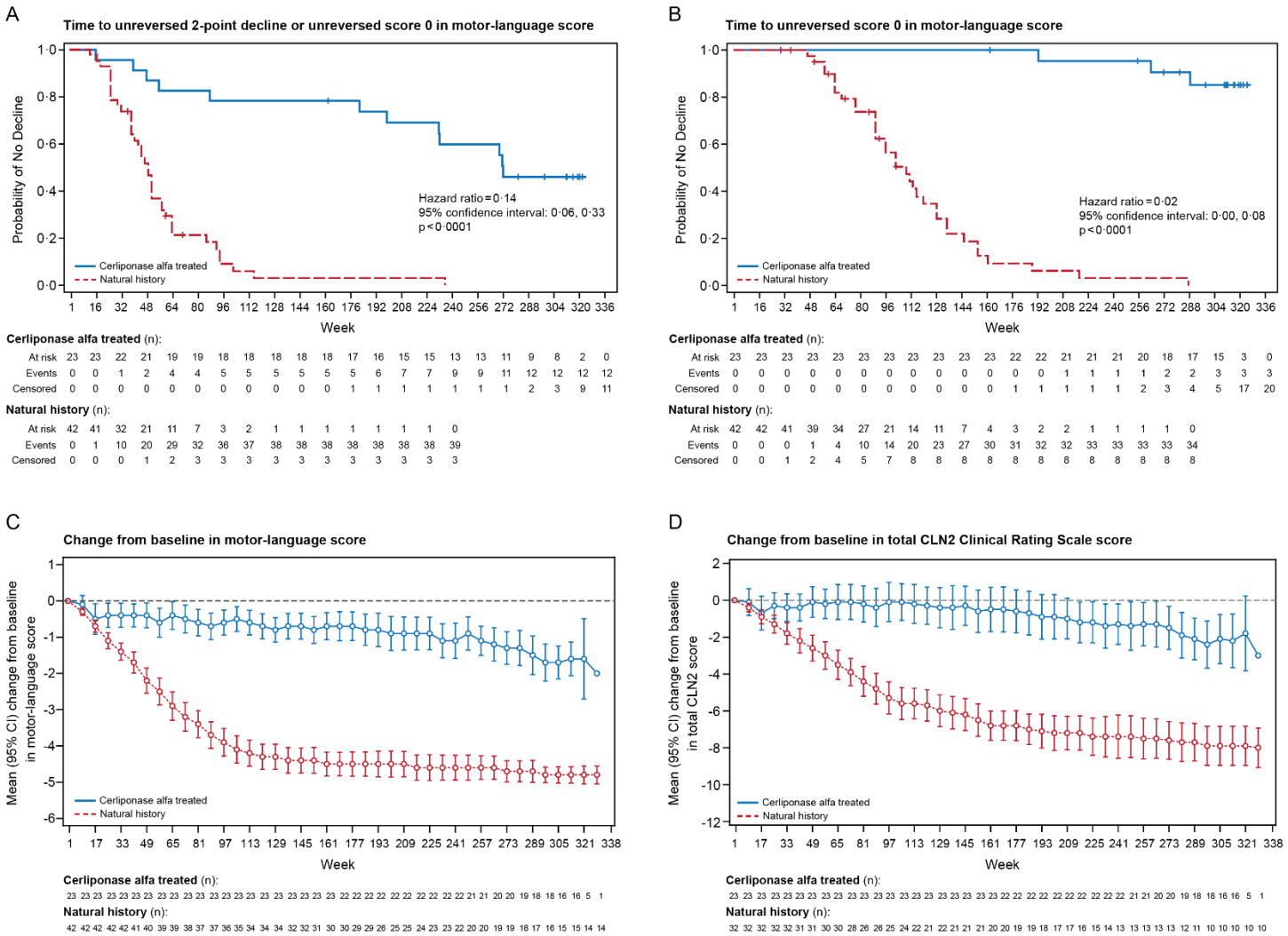
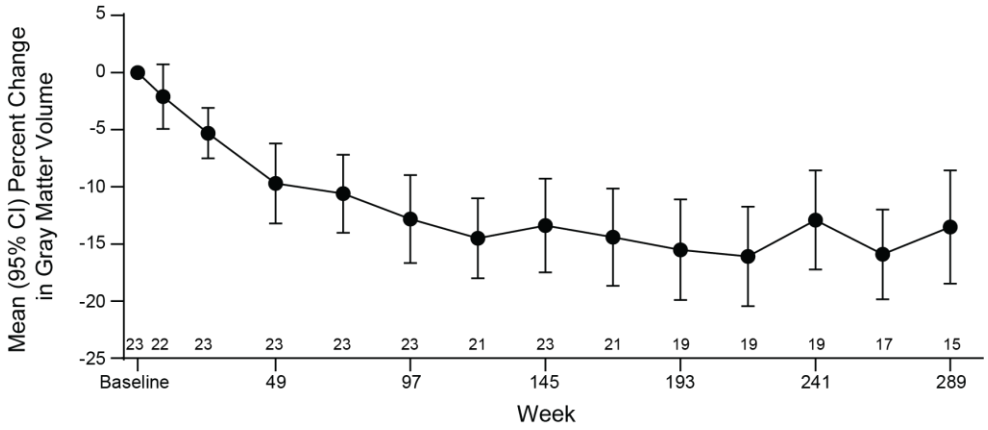

A
Time to unreversed 2-point decline or unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·14
95% confidence interval: 0·06, 0·33
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 22 21 19 19 18 18 18 18 18 17 16 15 15 13 13 11 9 8 2 0
Events 0 0 1 2 4 4 5 5 5 5 5 5 6 7 7 9 9 11 12 12 12 12
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 2 3 9 11
Natural history (n):
At risk 42 41 32 21 11 7 3 2 1 1 1 1 1 1 1 0
Events 0 1 10 20 29 32 36 37 38 38 38 38 38 38 38 39
Censored 0 0 0 1 2 3 3 3 3 3 3 3 3 3 3 3
B
Time to unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·02
95% confidence interval: 0·00, 0·08
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 23 23 23 23 23 23 23 23 23 22 22 21 21 21 20 18 17 15 3 0
Events 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 2 2 3 3 3
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 2 3 4 5 17 20
Natural history (n):
At risk 42 42 41 39 34 27 21 14 11 7 4 3 2 2 1 1 1 1 0
Events 0 0 0 1 4 10 14 20 23 27 30 31 32 32 33 33 33 33 34
Censored 0 0 1 2 4 5 7 8 8 8 8 8 8 8 8 8 8 8 8
C
Change from baseline in motor-language score
Mean (95% CI) change from baseline in motor-language score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 18 18 16 16 5 1
Natural history (n):
42 42 42 42 42 41 40 39 39 38 37 37 36 35 34 34 34 32 32 31 30 30 29 29 26 25 25 24 23 23 22 20 20 19 19 18 17 16 15 15 14 14
D
Change from baseline in total CLN2 Clinical Rating Scale score
Mean (95% CI) change from baseline in total CLN2 score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 19 18 18 16 16 5 1
Natural history (n):
32 32 32 32 32 31 31 30 30 30 28 26 26 25 24 22 21 22 21 21 21 20 20 19 19 18 17 17 16 15 14 13 13 13 13 13 12 11 10 10 10 10 10

Figure 2



Gray Matter Volume	Baseline	49 weeks	97 weeks	145 weeks	193 weeks	241 weeks	289 weeks
Mean (SD) volume, cm^3	452·0 (87·7)	408·3 (88·5)	394·6 (89·3)	390·3 (84·3)	374·2 (89·9)	390·4 (78·4)	371·9 (54·6)
Mean % change from Baseline	-	-10%	-13%	-13%	-16%	-13%	-14%
Annualized % change from Baseline	-	-11%	-14%	-15%	-17%	-14%	-15%
Annualized interval % change	-	-11%	-4%	-1%	-3%	+2%	+1%

Editors' Comments:

1. Please clarify in your manuscript that the supportive analyses for the primary outcome were prespecified.
   We have updated the text to state that the supportive analyses of the primary outcome were prespecified (line 199)
2. You state that data on whole brain percent gray matter are presented for the secondary outcome. Please clarify why this measure was selected and whether other data will be presented elsewhere.
   We have added to the text in the Outcomes section of the Methods to explain the selection of whole brain percent gray matter for inclusion (lines 209-212)
3. Please clarify in your manuscript which exploratory endpoints are not reported with a brief explanation why, for transparency.
   We have added the requested explanation to the manuscript text (lines 218-225)
4. Please add a statement to your contributors' section to clarify data access and verification, as confirmed in your previous response to editors' comments.
   This statement was previously included in the Role of the Sponsor section of the Methods but has now been moved to the Contributors' section at the end of the manuscript (lines 498-501).

Reviewers' Comments:

Reviewer #2:
The authors have provided additional information as supplementary material in response to my previous review. The information is interesting and is deserving of some discussion. Although there are no comparison data, the decline in almost every domain of the PedsQL warrants discussion. I think it is an important finding that QOL declines despite treatment that prolongs life and slows disease progression. Not discussing these data seems somewhat disingenuous to me.
We have added a section to the discussion on the QOL findings, as requested by the reviewer (lines 443-451).

Reviewer #3:
There are some major comments in the added sections in the Supplementary Materials which should be addressed.
1) Supplementary Materials, page 6, second paragraph, lines 1 and 5: Unrealistically large hazard ratio estimates (e.g., 0.04) and confidence limits (e.g., 0.00), though obtained from penalization methods, suggest sparse-data bias which should be highlighted as an important limitation of the study in the Discussion e.g., see the following paper:
Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. bmj. 2016 Apr 27;352.
We have added a sentence highlighting sparse-data bias as a potential limitation to the Discussion and cite the paper highlighted by the reviewer (lines 481-482).

2) Supplementary Materials, page 6, second paragraph, line 2: For the variable age of death, please report IQR along with median instead of 95% CI.
We have replaced the 95% CI with IQR for both age of death and time to death (Supplementary Materials page 6, second paragraph).

3) Tables S3-5, etc: Depending on the distribution, please report either mean (SD) or median (IQR) for description of quantitative variables.

We have added the IQRs to Tables S3-5 in the Supplementary Materials; given the small number of patients in this study, we believe that reporting both mean (SD) and median (IQR) is appropriate and provides the complete information for the reader.

Figure 1

Figure 2

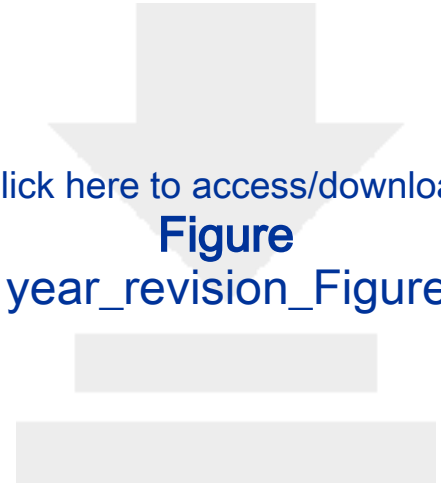


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Figure

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Figure S1

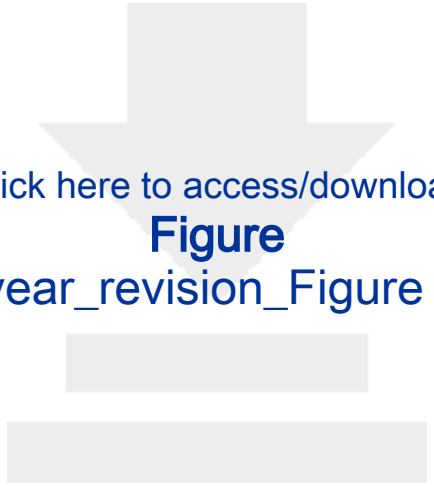

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Figure S2

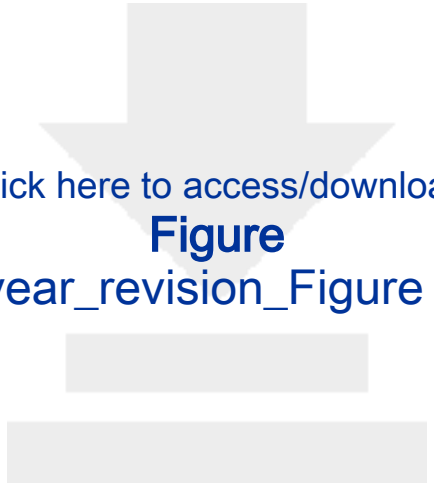

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Figure S3

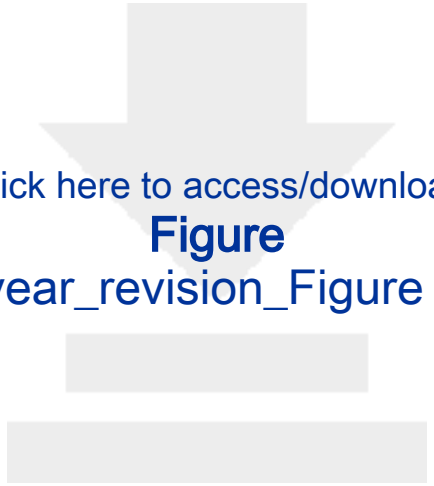

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Figure S4

Figure S5

Figure S6

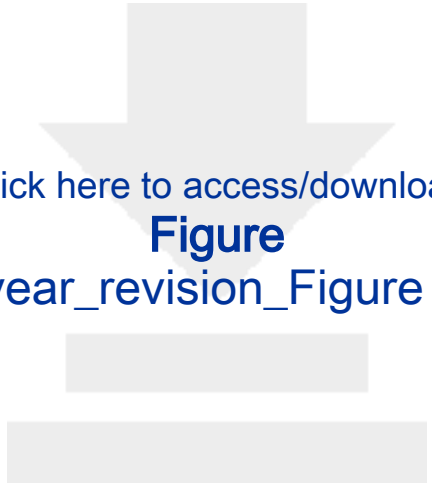

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Figure S7

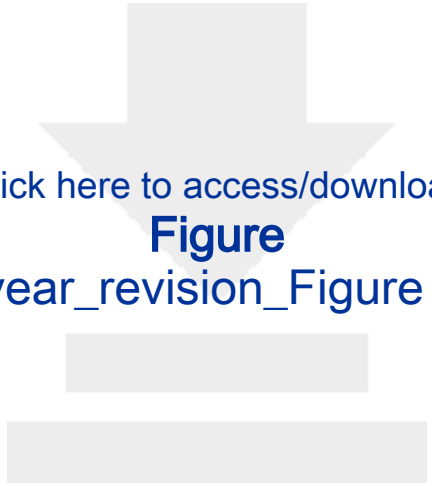

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Figure S8

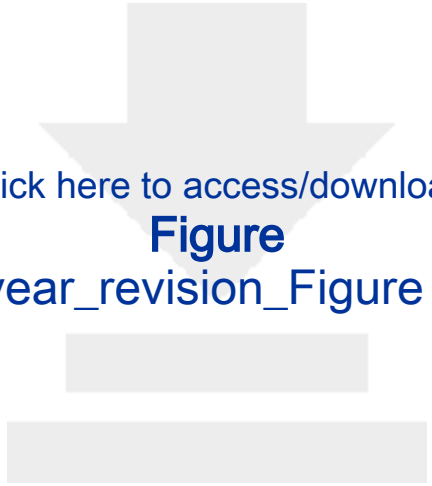

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Figure S9

Figure S10

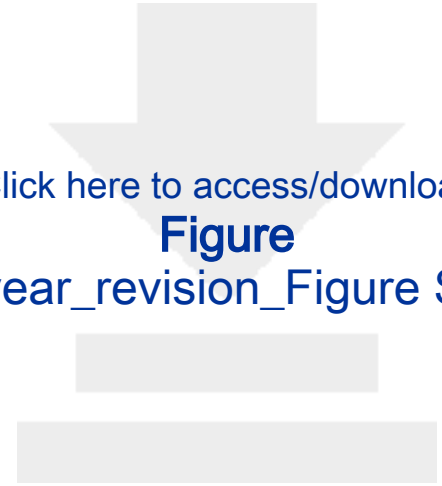

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Figure

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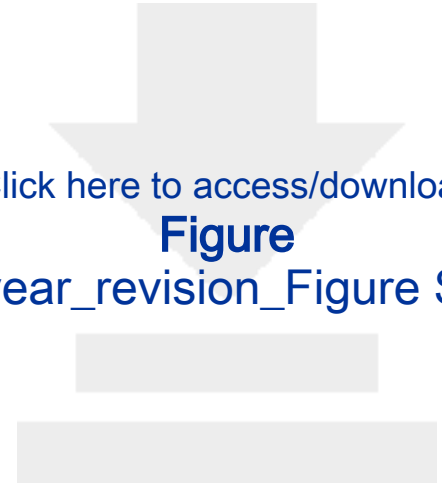
Figure S11



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CLINICAL STUDY PROTOCOL

Study Title:	A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease
Protocol Number:	190-202
Active Investigational Product:	Cerliponase alfa (BMN 190), recombinant human tripeptidyl peptidase 1 (rhTPP1)
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	IND 122472 / EudraCT 2014-003480-37
Indication:	CLN2 disease due to tripeptidyl peptidase 1 (TPP1) deficiency
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2 Extension
Sponsor's Responsible Medical Monitor:	Temitayo Ajayi, MD Sr. Medical Director, Rare Disease
Study Design:	Open-label Extension
Duration of Subject Participation:	Up to 240 weeks
Dose:	300 mg BMN 190 every-other-week
Study Population:	Patients with confirmed diagnosis of CLN2, who completed participation in 190-201
Date of Original Protocol:	3 October 2014
Date of Protocol Amendment 1:	12 August 2015
Date of Protocol Amendment 2:	16 November 2015
Date of Protocol Amendment 3:	26 February 2016
Date of Protocol Amendment 4:	17 March 2017
Date of Protocol Amendment 5:	05 May 2017
Date of Protocol Amendment 6	17 December 2018

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 6

Date: 17 December 2018

SUMMARY OF CHANGES AND RATIONALE

This section provides a numbered list of all significant changes and supporting rationale.

1. Updates were made to the immunogenicity assessment section to include serum neutralizing antibodies (NAb) sample collection. This change was made in response to a Regulatory Agency request to evaluate the presence of neutralizing antibodies to BMN 190 in serum. No changes are being made to the frequency or schedule of assessments.
2. Added clarification that for subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week device safety follow-up visit 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.
3. Re-classified electroencephalogram (EEG) from the list of safety assessment to efficacy assessments as this test provides information regarding changes in electrical activity in the brain while on study drug, but does not provide safety information used to determine whether dose modification or interruption is warranted.
4. Added that central laboratories (or a central reviewer) will be used to evaluate EEG scans in order to standardize review and data presentation, and limit site-associated variability.
5. Added CLN2 disease rating scale assessment to the 4-week device safety follow-up visit and 6-month safety follow-up visit in order to ascertain whether there were any functional changes associated with any reported adverse events.
6. Added ophthalmology/visual acuity assessment every 12 weeks and optical coherence tomography every 24 weeks in order to provide additional data to supplement the vision domain of the CLN2 rating scale.
7. Removed EQ-5D-5L Questionnaire in order to decrease study burden and the determination that the other Quality of Life questionnaires administered may be more relevant to this patient population.

8. Frequency of complete physical examination was changed from every 12 weeks to every 48 weeks to decrease burden to the subjects. The frequency of the brief physical exam remains unchanged (every 2 weeks). Assessment of height and body weight has been changed from every 48 weeks to every 24 weeks to permit additional monitoring of growth milestones.
9. Added updated information that the 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.
10. Clarified the stopping criteria that 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.
11. Clarified that, in the event of a device-related AE where the device and its components should be returned to BioMarin for further testing, the infusion pump does not need to be returned.
12. Updated Introduction to reflect interim 96-week results from the ongoing extension study (190-201 and 190-202).
13. Administrative changes have been made for consistency and clarity.

Refer to Section 0 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	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**
TITLE OF STUDY: A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease		
PROTOCOL NUMBER: 190-202		
STUDY SITES: Approximately 10 centers worldwide		
PHASE OF DEVELOPMENT: Phase 1/2 Extension		
STUDY RATIONALE: BMN 190 is a recombinant form of human tripeptidyl peptidase 1 (TPP1), the enzyme deficient in patients with CLN2 disease (also known as classical late-infantile CLN2, cLINCL, or Jansky-Bielschowsky disease), a form of Batten Disease. As an enzyme replacement therapy (ERT), BMN 190, is expected to restore TPP1 enzyme activity. Given the urgent and severe unmet medical need in CLN2 disease and observations 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. ERT with BMN 190 administered intrathecally or via intracerebroventricular infusion in both models yielded pharmacologically significant benefit. Furthermore, when dosing of BMN 190 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. There is currently no accepted, standard treatment for CLN2 other than supportive care. Enzyme replacement therapy (ERT) with BMN 190, or recombinant human TPP1 (rhTPP1), is a potential new treatment option for CLN2 patients. BMN 190 is expected to reduce the progressive, pathologic accumulation of lysosomal storage material, and improve the symptoms of disease. The Phase 1/2 study (190-201) evaluated the efficacy and safety of doses up to 300 mg/every other week (qow) BMN 190 in patients with CLN2. 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		

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	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

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.

The dose and regimen for this study (190-202) are based on the results of the 190-201 study. The rationale for this phase 2 extension study is to provide patients who complete the 190-201 study with the option to continue BMN 190 treatment. The 190-202 study is an open label extension protocol to assess long-term safety and efficacy.

OBJECTIVES:

The primary objective of the study is:

- To evaluate the long-term safety of BMN 190 administration at 300 mg qow in patients with CLN2.
- To assess change in motor and language (ML) subscales of the CLN2 disease rating scale in patients with CLN2 receiving BMN 190 at 300 mg qow.

The secondary objectives of the study are:

- To assess changes in quantitative assessment of MRI.
- To assess change in CLN2 disease scale total score.
- To evaluate quality of life (QoL) with long-term BMN 190 administration.

The exploratory objective of the study is:

- To evaluate age-appropriate developmental milestones with long-term BMN 190 administration.
- To evaluate the impact of treatment on disease-related biomarkers from CSF and blood.

STUDY DESIGN AND PLAN:

This is a multi-center, multinational, extension study to evaluate BMN 190 treatment in patients with CLN2 who completed 190-201. All patients who have completed 48 weeks in Study 190-201 will be eligible to enroll in Study 190-202.

The Screening period for Study 190-202 will start simultaneously with the Week 47 visit in Study 190-201. Baseline values for Study 190-202 will be recorded at the first infusion, Week 1 Day 1 of Study BMN 190-202, for all patients on active treatment. The first dose of BMN 190 in Study 190-202 (Week 1/Study Day 1) will be given following the Week 49 study assessments in Study 190-201. This study will be open label with all patients continuing on treatment with BMN 190 300 mg qow.

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Patients will complete safety and efficacy assessments including CSF surveillance labs every 2 weeks, CLN2 disease scales every 8 weeks, clinical laboratory assessments, visual acuity tests, and immunogenicity tests every 12 weeks. MRI, quality of life measures, OCT, EEG, developmental milestones (Denver II), and blood and CSF samples for evaluating disease-related biomarkers will be collected every 24 weeks. Complete physical examination will be performed every 48 weeks.

Some patients may experience hypersensitivity reactions, thus prophylactic antihistamine and/or antipyretic may be administered prior to each study drug infusion at the investigator's discretion. 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 Electronic Case Report Forms (eCRFs) and source files.

Patients may withdraw voluntarily from receiving study drug at any time, yet will be encouraged to continue to undergo study assessments. Patients may also withdraw entirely from complete study participation at any time, upon request.

NUMBER OF PATIENTS PLANNED:

All patients who complete 48 weeks in the 190-201 study may be eligible to enroll.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

To be eligible for study participation, a patient must meet all of the following inclusion criteria:

- Must have completed 48 weeks in Study 190-201.

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- Is willing and able to provide written, signed informed consent. Or, in the case of patients under the age of 18 (or other age as defined by regional law or regulation), provide written assent (if required) and have written informed consent, signed by a legally authorized representative, after the nature of the study has been explained, and prior to performance of research-related procedures.
- 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.
- If female, of childbearing potential, must have a negative pregnancy test at the Screening Visit and be willing to have additional pregnancy tests done during the study.

If any of the following exclusion criteria apply, a patient will not be eligible to participate in the study:

- Has had a loss of 3 or more points in the combined motor and language components of the Hamburg CLN2 rating scale between Baseline of Study 190-201 and the Study Completion visit in Study 190-201 and would not benefit from enrolling in the study in the Investigator's discretion.
- Has a score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale.
- Is pregnant or breastfeeding, at Baseline, or planning to become pregnant (self or partner) at any time during the study.
- Has used any investigational product (other than BMN 190), or investigational medical device, within 30 days prior to Baseline; or is required to use any investigational agent prior to completion of all scheduled study assessments.
- Has a concurrent disease or condition that would interfere with study participation, or pose a safety risk, as determined by the Investigator.
- Has any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study.

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INVESTIGATIONAL PRODUCT, DOSE, ROUTE AND REGIMEN:

All study subjects will be administered BMN 190 300 mg by ICV infusion every other week (preferably in the morning). Fasting for a minimum of 2 hours before each infusion may be considered until the subject's reaction to the study drug is determined. When a feeding tube is used for an overnight feed, the tube may be turned off 2 hours before infusion.

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.

DURATION OF TREATMENT:

Patients will receive qow ICV infusions of study drug, up to Week 239 or until one of the following occurs: the patient withdraws consent and discontinues from the study; the patient is discontinued from the study at the discretion of the Investigator; the patient enrolls in another study or registry; or the study is terminated.

CRITERIA FOR EVALUATION:

Safety:

- AEs and concomitant medication
- routine clinical laboratory tests (hematology, chemistry, and urinalysis)
- routine CSF surveillance (cell, count, protein, and glucose)
- vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, respiration rate, and temperature)
- physical examination (including height)
- 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:

- CLN2 disease rating scales with videotaping
- Total cortical grey matter volume
- Quality of Life surveys
- Developmental assessments
- Disease-related biomarkers
- EEG, standard awake
- Assessments of visual acuity
- Optical coherence tomography

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Immunogenicity:

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

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.

Safety and efficacy data will be merged and summarized with data from Study 190-201 to characterize the safety and efficacy of longer-term treatment. Safety assessments include adverse events, clinical laboratory results, vital signs, ECGs, and immunogenicity. Efficacy data include CLN2 assessments and MRI measurements of brain volumes.

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4 ABBREVIATIONS

AE	adverse event
CBC	complete blood count
CFR	Code of Federal Regulations
CLN2	late-infantile neuronal ceroid lipofuscinosis 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
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
ERT	enzyme replacement therapy
EU	European Union
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
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IP	investigational product
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
MRS	magnetic resonance spectroscopy
NAb	neutralizing anti-TPP1 antibody
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
OCT	optical coherence tomography
PD	pharmacodynamics

PedsQL	measurement model for Pediatric Quality of Life Inventory
PICU	pediatric intensive care unit
PK	pharmacokinetics
PLT	Preferential Looking Test
qow	every other week
REB	Research Ethics Board
SAE	serious adverse event
SAR	serious adverse reaction
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TAb	total anti-TPP1 antibody
TPP1	tripeptidyl peptidase 1
US	United States

Definition of Terms:

Investigational Product (IP):

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

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

Investigators are expected to interact with Ethics Committees (ECs) promptly, as required, during the course of the study. This includes, but is not limited to, providing appropriate documentation to support study initiation and maintaining appropriate flow of safety and other information during the course of the study and for study close-out activities. BioMarin (or designee) will assist Investigators with access to timely and accurate information and with 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 Board (REB) (for Canadian protocols), is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/EC/REB will be provided to BioMarin Pharmaceutical Inc. (BioMarin) or its designee.

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

5.2 Ethical Conduct of Study

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

This study will be conducted in accordance with the following:

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

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

5.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), United States (US) Code of Federal Regulations (CFR) 21 CFR §50, Directive 2001/20/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/EC/REB approval. BioMarin and the IRB/EC/REB must approve the documents before they are implemented. A copy of the approved ICF (minor assent form and parental ICF for studies involving minors), and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

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

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

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

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

7 INTRODUCTION

CLN2 disease, also known as late-infantile neuronal ceroid lipofuscinosis, NCL type 2 or Jansky-Bielschowsky disease, is a form of Batten Disease, a group of rare fatal pediatric dementias. CLN2 is caused by the deficiency of TPP1, resulting from mutations in the *CLN2* gene. TPP1 functions in the cell lysosome to cleave N-terminal tripeptides from a number of substrates. In the absence of TPP1, materials normally metabolized by this enzyme form abnormal autofluorescent inclusions in cell lysosomes. The CNS is uniquely susceptible to this process and the disease manifests as a neurodegenerative disorder and, ultimately, death. The onset of clinical symptoms is typically between ages 2 and 4 (Chang, 2011); (Kurachi, 2000) with an average age of diagnosis of 4 years. Patients typically present initially with seizures, followed by ataxia, myoclonus, impaired speech, cognitive impairment, and developmental regression. A decline in vision and motor skills follows, with patients blind and wheelchair bound by approximately 6 to 8 years of age. Patients enter into a vegetative state during the later stages of the disease and feeding and tending to everyday needs become very difficult. Disease progression is very rapid with death typically occurring between 10 and 15 years of age.

7.1 Nonclinical Studies

Nonclinical studies indicate likely therapeutic benefit without significant risk of BMN 190-related toxicity for patients with CLN2 disease. In CLN2 disease animal models, after either intracerebroventricular (ICV) or intrathecal (via the cisterna magna and lumbar spine) administration, BMN 190 reduced lysosomal storage, attenuated functional decline, delayed disease progression, and extended lifespan. In TPP1 KO mice, restoration of TPP1 enzyme activity reduced lysosomal storage accumulation, improved motor function, and extended lifespan (Sleat, 2008); (Xu, 2011). In TPP1-null dachshunds, BMN 190 also reduced lysosomal storage, preserved function, and extended lifespan; in addition, onset of neurodegenerative clinical signs was delayed or prevented (Vuillemenot, 2011); (Katz, 2014) BMN 190-10-077). Studies in cynomolgus monkeys have indicated widespread distribution of active enzyme in the CNS after ICV infusion and no drug-related safety findings (Vuillemenot, 2014).

BMN 190 concentrations in cerebrospinal fluid (CSF) remained above the lysosomal K_{uptake} for approximately 48 hours after single ICV or intrathecal infusions in species (dog and monkey) with CSF dynamics similar to those in human (Study BMN 190-09-071; Study BMN 190-10-077; Study BMN 190-11-046; Vuillemenot, 2014). In these same species, CNS distribution of BMN 190 was extensive in many brain regions. Distribution and PK

characteristics after ICV infusion of BMN 190 appear even more advantageous than intrathecal administration for treatment of CLN2 disease. A mean CNS half-life of approximately 2 weeks (range, 3.1 to 87.2 days, depending on CNS site) (BMN 190-09-071) suggests biweekly dosing may sustain therapeutic BMN 190 levels in the CNS.

Considered collectively, toxicology data have not identified any drug-related safety issues when BMN 190 is administered by ICV or intrathecal 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 (BMN 190-10-077) and was largely attributable to the implanted catheters and infusion procedure; vehicle-treated and wild-type treated animals exhibited the same findings. Hypersensitivity reactions in dachshunds following repeated BMN 190 administration, correlating with systemic exposure and anti-BMN 190 antibody titers, were attributed to the canine immune response to human heterologous protein and were clinically manageable with infusion time extension (BMN 190-10-077). Systemic toxicity due to exaggerated pharmacology is unlikely since BMN 190 is the inactive pro-form of human TPP1 that requires lysosomal uptake for activation. Also, the bulk of ICV-administered BMN 190 remains in the CNS.

Maximum ICV dose levels for monkey and dachshund studies were based on upper limits of BMN 190 concentration at the time of study initiation, infusion rate, and infusion time. Infusion conditions were selected to minimize effects on intracranial pressure due to rapid changes in CSF volume as well as to minimize the anesthetization period needed for the infusion procedure. Extension of the infusion time from 2 hours (at 0.6 mL/hour) to 4 hours (at 0.3 mL/hour) mitigated hypersensitivity reactions in dachshunds. An amount equivalent to approximately 5% of the total CSF volume was infused per hour in dog and monkey studies. Thus, the maximum feasible ICV doses were 16 mg/dose for dog (BMN 190-10-077) and 20 mg/dose for monkey (BMN 190-09-071).

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 tripeptidyl peptidase 1(TPP1), the enzyme deficient in patients with CLN2 disease (also known as classical late-infantile CLN2, cLINCL, or Jansky-Bielschowsky disease), a form of Batten Disease. As an enzyme replacement therapy (ERT), BMN 190, is expected to restore TPP1 enzyme activity. Given the urgent and severe unmet medical need in CLN2 disease and observations 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).

There is currently no accepted, standard treatment for CLN2 other than supportive care. Enzyme replacement therapy (ERT) with BMN 190, or recombinant human TPP1 (rhTPP1), may be a potential new treatment option for CLN2 patients. BMN 190 is expected to reduce the progressive, pathologic accumulation of lysosomal storage material, and improve signs and symptoms of the disease.

The Phase 1/2 study (190-201) evaluated the efficacy and safety of doses up to 300 mg/every other week (qow) BMN 190 in patients with CLN2 disease. 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.

The dose and regimen for this study (190-202) are based on the results of the 190-201 study. The rationale for this phase 2 extension study is to provide patients who complete the 190-201 study with the option to continue BMN 190 treatment. The 190-202 study is an open label extension protocol to assess long-term safety and efficacy.

7.4 Summary of 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 10.3.

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 10.1.

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 assessed to be hypersensitivity reactions. It is expected that the adverse events of greatest clinical importance will be immune-mediated hypersensitivity reactions, but not all hypersensitivity reactions 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 have had an ICV reservoir surgically implanted for administration of BMN 190. The use of ICV devices may 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). Although these devices have been approved for use for decades, there is little available safety data for long term use.

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 (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 needed 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 (refer to Section 9.7.6.2). 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 BMN 190; with the decision made on an individual subject level based on the medical judgment of the Investigator.

All BMN 190 infusions are given in an inpatient setting with supportive measures present. A follow-up phone call will be conducted ~48 hours after the patient has been discharged from each infusion visit.

8 STUDY OBJECTIVES

The primary objective of the study is:

- To evaluate the long-term safety of BMN 190 administration at 300 mg qow in patients with CLN2.
- To assess change in motor and language (ML) subscales of the CLN2 disease rating scale in patients with CLN2 receiving BMN 190 at 300 mg qow.

The secondary objectives of the study are:

- To assess changes in quantitative assessment of MRI.
- To assess change in CLN2 disease scale total score.
- To evaluate quality of life (QoL) with long-term BMN 190 administration.

The exploratory objectives of the study are:

- To evaluate age-appropriate developmental milestones with long-term BMN 190 administration.
- To evaluate the impact of treatment on disease-related biomarkers from CSF and blood.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multi-center, multinational, extension study to evaluate BMN 190 treatment in patients with CLN2 who completed 190-201. All patients who have completed 48 weeks in Study 190-201 will be eligible to enroll in Study 190-202.

The Screening period for Study 190-202 will start simultaneously with the Week 47 visit in Study 190-201. Baseline values for Study 190-202 will be recorded at the first infusion, Week 1 Day 1 of Study BMN 190-202, for all patients on active treatment. The first dose of BMN 190 in Study 190-202 (Week 1/Study Day 1) will be given following the Week 49 study assessments in Study 190-201. This study will be open label with all patients continuing on treatment with BMN 190 300 mg qow.

Patients will complete safety and efficacy assessments including CSF surveillance labs every 2 weeks, CLN2 disease scales every 8 weeks, clinical laboratory assessments, visual acuity tests, and immunogenicity tests every 12 weeks. MRI, quality of life measures, OCT, EEG, developmental milestones (Denver II), and blood and CSF samples for evaluating disease-related biomarkers will be collected every 24 weeks. Complete physical examination will be performed every 48 weeks.

Some patients may experience hypersensitivity reactions associated with the administration of study drug, thus prophylactic antihistamine may be administered prior to each study drug infusion at the discretion of the Investigator. Antipyretic pretreatment may be given at the Investigator's discretion. Vital signs will be measured just before, during, and immediately following the study-drug infusion. Adverse events and changes in concomitant medication will be recorded throughout the study.

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 10.6) 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 Electronic Case Report Forms (eCRFs) and source files.

Patients may withdraw voluntarily from receiving study drug at any time, and they may also withdraw entirely from complete study participation at any time, upon request. If BMN 190 treatment is suspended, BMN 190 may resume if no more than 2 consecutive doses are missed after the last given dose.

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

Table 9.1.1: Schedule of Events

Assessments and Events	Screening Period (2 weeks)	Q2 Weeks ± 3 days	Q8 Weeks ± 3 days	Q12 Weeks ± 3 days	Q24 Weeks ± 3 days	Q48 Weeks ± 3 days	Study Completion or ETV (2 weeks) ± 3 days after Week 239	Device Safety Follow-Up (4 weeks after device removal) ± 3 days	Safety Follow-Up (6 months after last dose) ±1 week
Informed consent/assent[a]	X								
Criteria for study entry[b]	X								
Medical history[c]		X (Week 1 only)							
CLN2 disease rating scales[d]			X				X	X	X
Videotaping of CLN2 scales[d]					X		X		
Visual acuity testing[e]				X			X		
Optical coherence tomography[f]					X		X		
ECG (3- or 5-lead)[g]		X[g]							
ECG (12-lead)[h]		X			X		X		X
EEG, standard awake[i]					X		X		X
MRI[j]					X		X		
CSF (cell count, protein, glucose, culture)[k]		X					X		
Device Patency/Infection[l]		X							
Administer study drug		X							
Phone follow-up[m]		X							
CSF/blood for disease-related biomarkers[n]					X		X		
CSF/serum for immunogenicity[o]				X			X	X	X

Assessments and Events	Screening Period (2 weeks)	Q2 Weeks ± 3 days	Q8 Weeks ± 3 days	Q12 Weeks ± 3 days	Q24 Weeks ± 3 days	Q48 Weeks ± 3 days	Study Completion or ETV (2 weeks) ± 3 days after Week 239	Device Safety Follow-Up (4 weeks after device removal) ± 3 days	Safety Follow-Up (6 months after last dose) ±1 week
								(serum only)	(serum only)
Vital signs[p]		X					X	X	X
Height/weight					X		X		X
Complete physical examination[q]						X	X		X
Brief physical examination[r]		X						X	
Blood/urine for clinical lab tests[s]				X			X	X	X
CLN2 specific QoL questionnaire[t]					X		X		
PedsQL[t]					X		X		
Denver II Developmental Scale[u]					X		X		
Neurological examination				X			X	X	
Pregnancy testing (in females of childbearing potential)[v]	X								
Adverse events[w]	X	X					X	X	X
Concomitant medications	X	X					X	X	X
Hypersensitivity labs		X[x]							
ICV Access device removal							X[y]		

Baseline values will be recorded at the time of the first infusion, Week 1 Day 1 of Study BMN 190-202. Thereafter, study visits will be every two weeks ±3 days. If done on the same day, assessments of function and QoL should precede MRI and blood and CSF 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 7 days.

[a] Written informed consent must be obtained before study procedures begin.

[b] Two domains (motor and language) of the Hamburg Scale will be tested for eligibility to enroll in 190-202. Subjects must not have had a loss of 3 or more points in the combined motor and language components at the end of 190-201 compared with 190-201 Baseline, and they also must not have a score of 0 on the combined motor and language components of the CLN2 rating scale.

[c] Medical History to be collected during Week 1 only, and prior to receiving the first dose on 190-202. Any ongoing AEs/SAEs in 190-201 will be documented as medical history in 190-202.

[d] All domains of both Hamburg Scale and Weill Cornell Scale will be tested every 8 weeks during the study through study completion (or within one week of Early Termination visit), at the 4-week Device Safety follow-up, and at the 6-month Safety follow-up visit. If done on the same day, assessments of function and QoL should precede MRI and blood and CSF sampling. Videotaping of the CLN2 disease scale evaluation will occur every 24 weeks when the CLN2 disease scale is assessed, at any time a Termination from the study is warranted, and at the first visit for all new sites.

[e] 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.

[f] 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.

[g] For at least one infusion of BMN 190 (and preferably the next 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. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG.

[h] 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.

[i] EEG values will be recorded within 2 days before each infusion at the specified time points.

[j] MRI assessment should precede blood and CSF sampling. A ±4-week window is allowed for this assessment and may be performed at the same time as a scheduled infusion.

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

[l] 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.

[m] Parent/guardian will be telephoned ~48 hours for follow-up after having been discharged from each visit to document health status and to remind them to initiate contact if any symptom of concern is observed. At a minimum, the telephone follow up will include guidance for the parent or legal guardian to detect clinical signs of an infection of the ICV reservoir and meningitis or encephalitis.

[n] Samples of blood and CSF will be collected prior to infusion.

[o] Samples of blood (serum) and CSF will be collected for TAb and NAb testing before the first infusion (Study 190-201 Study Completion Visit), every 12 weeks thereafter, and at the Study Completion Visit of Study 190-202. 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. Serum and CSF NAb will be tested prior to the first infusion (Study 190-201 Study Completion Visit) and at subsequent time points when serum and CSF TAb are positive, respectively. Samples from the Study Completion visit in Study 190-201 will be used to obtain a baseline

total and drug-specific IgE levels in the event of later hypersensitivity reactions requiring additional lab work. Samples of blood (serum) only will be collected for TAb, total IgE, C4, and tryptase as part of the Safety Follow-Up visit and the Device Safety Follow-Up visit; CSF will not be collected at either of these safety follow-up visits.

[p] 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.

[q] A complete physical examination will include general appearance, cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Clinically significant abnormalities will be recorded as AEs.

[r] A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, and gastrointestinal systems. Clinically significant abnormalities will be recorded as AEs.

[s] Samples for clinical laboratory assessments (hematology, chemistry, and urinalysis) will be collected before infusion.

[t] Quality of life assessments include 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 and sampling.

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

[v] During the Screening period, a female subject judged by the investigator to be of childbearing potential will be tested for pregnancy with a urine pregnancy test; additional urine tests will be performed during the study whenever pregnancy is in question. A serum pregnancy test will be performed if a urine test result is positive or equivocal.

[w] All AEs and SAEs will be recorded starting with the first dose of study drug in Study 190-202 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. Refer to Section 10.1 for AE and Section 10.2 for SAE reporting instructions for subjects who receive study drug in another BioMarin-sponsored study or registry within the 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] 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).

[y] Following either the study completion visit (Week 239) 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.

9.2 Discussion of Study Design, Including Choice of Control Group

Study 190-202 is designed to be an extension for patients who complete 48 weeks in Study 190-201. Natural history data as collected in Study 190-901 will be used as a control group for comparison.

9.3 Selection of Study Population

All patients who have completed 48 weeks in Study 190-201 will be eligible to enroll in Study 190-202.

9.3.1 Inclusion Criteria

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

- Must have completed 48 weeks in Study 190-201.
- Is willing and able to provide written, signed informed consent. Or, in the case of patients under the age of 18 (or other age as defined by regional law or regulation), provide written assent (if required) and have written informed consent, signed by a legally authorized representative, after the nature of the study has been explained, and prior to performance of research-related procedures.
- 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.
- If female, of childbearing potential, must have a negative pregnancy test at the Screening Visit and be willing to have additional pregnancy tests done during the study.

9.3.2 Exclusion Criteria

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

- Has had a loss of 3 or more points in the combined motor and language components of the Hamburg CLN2 rating scale between Baseline of Study 190-201 and the Study Completion visit in Study 190-201 and would not benefit from enrolling in the study in the Investigator's discretion.
- Has a score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale.
- Is pregnant or breastfeeding, at Baseline, or planning to become pregnant (self or partner) at any time during the study.

- Has used any investigational product (other than BMN 190 in 190-201), or investigational medical device, within 30 days prior to Baseline; or is required to use any investigational agent prior to completion of all scheduled study assessments.
- Has a concurrent disease or condition that would interfere with study participation, or pose a safety risk, as determined by the Investigator.
- Has any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study.

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 (ETV) should be completed (Section 12.6).

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. Subjects who discontinue from the study will have their reservoir and any associated hardware removed, unless doing so would be more harmful than not in the opinion of the Investigator or neurosurgeon.

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/REB. 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 10.1, 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.

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 of Subjects

Each subject will be assigned the same patient identifier that was used in Study 190-201, which will be on all eCRF pages. If the subject transfers primary study site between Study 190-201 and Study 190-202, the site number in the subject ID (first four numbers) will be updated, but the subject number (last four numbers) will remain the same. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used. Subjects who discontinue from the study for any reason will not be replaced.

9.3.5 Duration of Subject Participation

Patients will receive qow ICV infusions of study drug, up to Week 239 or until one of the following occurs: the patient withdraws consent and discontinues from the study; the patient is discontinued from the study at the discretion of the Investigator; or the study is terminated in the region where the patient is being followed.

A Safety Follow-Up visit will be conducted 6 months after the final BMN 190 infusion. The Safety Follow-Up visit will be waived for subjects who receive study drug in another BioMarin-sponsored study or registry within this 6-month period (refer to Section 10.1 and Section 10.2 for AE and SAE reporting instructions). For subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week device safety follow-up visit 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.

9.4 Treatments

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

9.4.1 Treatments Administered

All study subjects will be administered BMN 190 300 mg by ICV infusion every two weeks (preferably in the morning). Fasting for a minimum of 2 hours before each infusion may be considered until the subject's reaction to the study drug is determined. When a feeding tube is used for an overnight feed, the tube may be turned off 2 hours before infusion.

9.4.2 Identity of Investigational Product

9.4.2.1 Product Characteristics and Labeling

The study drug label includes 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 drug must be stored under conditions specified in the Investigator's Brochure and BioMarin provided Pharmacy Manual in a secure area accessible only to the designated pharmacists and clinical site personnel. All study drug 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

All study subjects will be administered BMN 190 300 mg by ICV infusion every two weeks (preferably in the morning). Fasting for a minimum of 2 hours before each infusion may be considered until the subject's reaction to the study drug is determined. When a feeding tube is used for an overnight feed, 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. Subjects should be closely monitored in an appropriate inpatient setting for up to 48 hours following the start of each infusion; if no safety issues are observed, a subject may be discharged 24 hours after the infusion begins. Because hypersensitivity reactions may be associated with ERT administration, subjects may be pretreated with age-appropriate doses of antihistamine (and antipyretic, if appropriate) medication approximately 30 minutes (± 15 minutes) before BMN 190 infusion at the discretion of the investigator. 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 infusions.

BMN 190 will be infused ICV at 2.5 mL/hour to deliver the entire volume over approximately 4 hours. 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.

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 190 300 mg every other week. Doses lower than 300 mg may be administered at the discretion of the Investigator and upon consultation with the Medical Monitor if required for safety or other reasons.

9.4.4.1 Safety Monitoring

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. A follow-up telephone call will be conducted ~48 hours after the subject has been discharged from the visit.

Vital signs (Section 9.7.6.1) will be measured at least at the following time points: 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 at least one infusion of BMN 190 (and preferably the next 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. 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 (Table 9.1.1). 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 or any adverse events 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 including anaphylaxis and other allergic reactions, refer to Section 10.3.

Symptoms of hypersensitivity reactions including anaphylaxis and other allergic 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). Based on previous hypersensitivity reactions, and with the approval of the medical monitor, additional blood samples may be required following subsequent hypersensitivity reactions. 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 7.3) 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 hypersensitivity 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 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 (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 needed 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. In the event that the device is replaced, the next drug infusion will occur at least 14 days and no more than 28 days from 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.

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. If the subject intends to continue to receive BMN 190 following participation in this study (eg., via commercial product, use in a registry, or another BMN 190 study), then the device does not need to be removed. A device removal safety follow-up visit will be performed within 4 weeks (±3 days) from removal of the ICV access device.

9.4.5 Method of Assigning Subjects to Treatment Groups

This is a single-arm study. All subjects will receive BMN 190 qow.

9.4.6 Selection of Doses Used in the Study

The planned dose level is 300 mg qow. This dose is based on data from Study 190-201.

The dose level is derived from dose levels used in the TPP1-null dachshund study (Katz, 2014) (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. Human-equivalent doses were calculated by two methods: CSF volume scaling and brain mass scaling. CSF volume for a child aged 2 to 7 years was estimated to be 100 mL, based on normal adult volumes of 125 to 250 mL; the scaling factor is 8-fold for a dachshund CSF volume of 12.5 mL. 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, yielding a scaling factor of 20-fold based on average dachshund brain mass of 50 g. Since TPP1 activity in brain tissue is more proximally related to CNS lysosomal storage materials, scaling by brain mass is judged to be more predictive of the human therapeutic dose.

The no-observed-adverse-effect level (NOAEL) from nonclinical studies in dachshund was 16 mg, which would correspond to 320 mg in human. Therefore, the starting dose of 30 mg in the preceding study (190-201) is more than 10-fold below the human equivalent of the nonclinical NOAEL.

The clinical experience of BMN 190 for this regimen is justified by the observed safety and tolerability of BMN 190 in Study 190-201 to date.

9.4.6.1 Selection of Timing of Dose for Each Subject

A mean CNS half-life of approximately 2 weeks (BMN 190-09-071) 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 intrathecal infusions in species with CSF dynamics similar to those in human (Vuillemenot, 2014), (Vuillemenot, 2011), (BMN 190-09-071). 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 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 approximately 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. To date, infusions at parameters listed above in patients in Study 190-201 have shown no safety concerns.

9.4.7 Blinding

This is an open-label study. Study site assessments of safety and clinical severity will be performed without blinding to treatment.

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

Ongoing medications taken during participation in BMN 190-201 should be recorded in the eCRF. Any concomitant medication added or discontinued during the study should be recorded in the eCRF (or within one week of the Early Termination visit).

It is anticipated that all subjects will be taking anticonvulsants. Subjects may also be taking medications for myoclonus, tremor, agitation, and pain. Investigators will be asked to keep these regimens constant from before the First Dose visit 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 IP(s) received, subjects to whom IP is dispensed (subject-by-subject dose specific accounting), and IP lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (on-site CRA) has confirmed the accountability data.

9.5.1 Return and Disposition of Clinical Supplies

Unused 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 the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to BioMarin upon request. 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.

9.7 Efficacy and Safety Variables

Although this study is designed to assess safety and tolerability primarily, efficacy will be assessed by impact on disease-specific clinical rating scales. MRI is being assessed as a secondary efficacy variable. Effect on quality of life (QoL), developmental milestones, disease-related biomarkers, EEG, visual acuity, and optical coherence tomography (OCT) will also be explored.

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

9.7.1 Primary Efficacy Variables

9.7.1.1 Disease-Specific Rating Scales

Disease severity has been evaluated by two CLN2 disease-specific rating scales: the Hamburg Scale (Steinfeld, 2002); (Worgall, 2008) and the Weill Cornell Scale (Dyke, 2012); (Worgall, 2007). Both scales consist of four domains with intrinsic content validity. Within each domain of both scales, 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 domains common to each rating scale, motor (Hamburg) or gait (Weill Cornell) and language, are most relevant to mild to moderate CLN2 disease (Section 9.2), they will be used to assess study eligibility and efficacy (**Error! Reference source not found.**). Timing of post-treatment administration of these rating scales is detailed in Table 9.1.1.

Raters will be identified as qualified practitioners, who have been trained on the definitions and implementation of the CLN2 disease rating scales. 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.

Rating scale assessments will be videotaped in a standardized manner across all study sites. The Ratings Assessment Guidelines provide detailed instructions for videotaping. Timing for videotaping of the CLN2 disease scale evaluations is detailed in Table 9.1.1.

9.7.2 Secondary Efficacy Variables

9.7.2.1 Magnetic Resonance Imaging

All image data will be acquired without contrast 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.

Timing of MRIs is detailed in Table 9.1.1.

An MRI scan also should be performed whenever infection or ICV port 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.

9.7.3 Exploratory Variables

9.7.3.1 Quality of Life Testing

Quality of life will be assessed using 2 different instruments: the PedsQL™ Measurement Model for Pediatric Quality of Life Inventory (PedsQL) and the CLN2-specific questionnaire.

The age-appropriate assessments for each instrument will be completed for all patients at the timepoints indicated in the Schedule of Events (Table 9.1.1).

9.7.3.1.1 PedsQL Measurement Model for Pediatric Quality of Life Inventory

The PedsQL™ Generic Core Scales (including both a Parent Report for Toddlers and a Family Impact Module) 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.

9.7.3.1.2 CLN-2 Specific Quality of Life Questionnaire

The CLN2 health related quality of life assessment 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.

9.7.3.2 Denver II Developmental Screening Test

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.

9.7.3.3 Biomarkers

Blood and CSF will be collected from subjects at the time points indicated inTable 9.1.1 and may be used to evaluate biochemical, molecular, cellular, and genetic aspects relevant to CLN2 disease. CSF and blood will be collected for exploratory biomarker research. Samples will be collected prior to 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 for other purposes may be used for exploratory use once the primary use has been completed.

9.7.3.4 Electroencephalogram

A standard awake EEG will be recorded within 2 days before each infusion as indicated in Table 9.1.1.

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 Week 1 and as an AE thereafter. Evaluation will be done both locally and by a centralized vendor.

9.7.3.5 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.

9.7.3.6 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.

9.7.4 Immunogenicity

Immunogenicity tests will be performed using validated immunogenicity assays on serum and CSF samples. Samples of CSF and serum will be collected for anti-BMN 190 TAb and NAb testing, as detailed in Table 9.1.1. Collection must precede study drug infusion when collected for routine immunogenicity assessments. Baseline blood (serum) samples will be collected at the Study Completion visit in Study 190-201 to obtain a baseline TAb and NAb, every 12 weeks thereafter (Q12W), at the Study Completion or Early Termination visit, at the Device Safety Follow-Up visit, and at the Safety Follow-Up visit. CSF samples will be collected for anti-BMN 190 TAb and NAb testing at the Study Completion visit in Study 190-201 and every 12 weeks thereafter (Q12W). Serum and CSF NAb will be tested at Study Completion Visit in Study 190-201 and at subsequent time points when serum and CSF TAb are positive, respectively. No CSF immunogenicity assessments will be performed at either of the safety follow-up visits.

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). At the Device Safety Follow-Up visit and the Safety Follow-Up visit, serum samples will be collected to assess total IgE, tryptase, and C4.

9.7.5 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, 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, protein, glucose, and culture), concomitant medications, and AE/SAEs reported during the study as related to the device will be monitored.

9.7.5.1 Adverse Events

AEs and SAEs will be recorded as defined in Section 10. At each visit, subjects will be asked about new or ongoing AEs since the previous visit.

9.7.5.2 Device Malfunction

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 10.3.

9.7.5.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for routine clinical laboratory assessments (blood chemistries, hematology, and urinalysis) as detailed in Table 9.1.1.

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 Week 1 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 eCRF.

Table 9.7.5.3.1: 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		

9.7.5.4 Cerebrospinal Fluid Surveillance

Samples of CSF for routine surveillance (cell count with differential, protein, glucose, and culture) will be collected within 30 (±5) minutes before every infusion (or within one week of the Early Termination visit), as indicated in Table 9.1.1.

9.7.5.5 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 as indicated in Table 9.1.1.

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

9.7.6.1 Vital Signs

Vital signs (SBP, DBP, heart rate, respiration rate, and temperature) will be measured as indicated in Table 9.1.1. For every infusion, 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.

9.7.6.2 Physical Examination

A complete physical examination will be performed as indicated in Table 9.1.1. A complete examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems (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). Results of the neurologic examination may also be used to assess the efficacy of BMN 190.

A brief physical examination will be performed otherwise, as indicated in Table 9.1.1.
A brief examination will include general appearance, cardiovascular, respiratory, neurologic, and gastrointestinal assessments.

Body weight and height assessments should be performed 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 revise 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 noted during physical examination will be recorded under Medical History at Week 1 or as AEs thereafter.

9.7.6.3 Electrocardiogram

For at least one infusion of BMN 190 (and preferably the next 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. 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.

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 Week 1 and as an AE thereafter.

9.7.6.4 Pregnancy Testing

A pregnancy test will be performed during the Screening period on female subjects of childbearing potential.

A female subject judged by the investigator to be of childbearing potential will be tested for pregnancy with a urine pregnancy test; additional urine tests will be performed during the study 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 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, etc.).

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.

All AEs/ SAEs/ adverse events of special interest (AEOSIs) / pregnancies will be recorded starting after the first dose of study drug in Study 190-202. Reporting of AEs/SAEs / AEOSIs/ pregnancies will continue until 6 months after either the last administration of study drug or the Early Termination visit. 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 follow-up visit 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 subjects who enroll into another BioMarin-sponsored study or registry, AE/SAE / AEOSI/ pregnancy reporting is as follows:

- The 190-202 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.

Criteria for determining and reporting SAEs is provided in Section 10.2.

For this study, a medical device is defined as the infusion pump and all contact parts components required for infusion (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 device AE/SAE eCRF and the device report form and reported to BioMarin Pharmacovigilance (BPV) within 24 hours by entering the event information via EDC and completing the study specific device report form(s). Prophylactic replacement of the ICV must be reported as a device related event. The reporting period for device-related events is the same as the reporting period for all AEs and SAEs; if the device is removed prior to the 6 month safety follow-up visit, the follow-up safety reporting period for device-related events is 4 weeks from the removal of the device.

The Investigator should follow all unresolved AEs until the events are resolved or 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. Outcome of AEs (with dates) should be documented on the appropriate eCRF page(s) and in the patient's medical record.

The Investigator responsible for the care of the patient or medically qualified designee will assess AEs for severity, relationship to study-drug, and seriousness (see Section 10.2 for SAE definition). 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.

10.1.1.1 Seriousness

The investigator will assess if an AE should be classified as "serious" based on the seriousness criteria enumerated in Section 10.2. Seriousness serves as a guide for defining regulatory reporting obligations.

10.1.1.2 Severity

The severity of each AE will be assessed using the defined categories in Table 10.1.1.2.1.

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 10.1.1.2.1: 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.

10.1.1.3 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 10.1.1.3.1.

Table 10.1.1.3.1: 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.

10.2 Serious Adverse Events

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

- Is fatal
- Is life threatening

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

The reporting period for SAEs begins after the first dose of study drug in Study 190-202 and continues until 6 months after either the last administration of study drug or the Early Termination visit. 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. Refer to Section 10.1 for additional information regarding SAE reporting for these subjects. For subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week device safety follow-up visit 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. If a subject is discontinued from the study prematurely, SAEs will be recorded at the Early Termination visit.

Exclusions to SAE reporting include planned hospitalization for a study procedure or elective surgery before study enrollment. Events that occur as a result of these hospitalizations or surgeries that meet SAE reporting requirements are reportable to BPV within 24 hours.

All SAEs, including device-related events, whether or not considered related to study drug, must be reported within 24 hours of the site becoming aware of the event. SAEs will be reported via eCRF to BPV. 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. Device and device component related events will also require completion of the study specific Device Report form and must be submitted to BPV within 24 hours. 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 Sponsor is responsible for identifying, preparing, and reporting all suspected unexpected serious adverse reactions (SUSARs) to the relevant competent authorities, ethics committees, and investigators in accordance with requirements identified in the Clinical Trials Regulations.

The investigator should follow any unresolved SAE until the event is resolved or stabilized, the subject is lost to follow-up, or it has been determined that study treatment or participation is not the cause of the SAE. Resolution of SAEs (with dates) should be documented in the eCRF and in the subject's medical record.

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

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

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

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

10.3 Adverse Events of Special Interest

AEOSIs may be assessed by the Investigator as serious or non-serious. AEOSIs for this study include status epilepticus, hydrocephalus (communicating and noncommunicating), meningitis, unexpected rapid decline on CLN2 disease scale not attributable to other causes, hypersensitivity, all device-related events (e.g., infection, malfunction with an associated AE such as leaking reservoir or a problem that ends the administration of study drug for that visit, etc.), cardiovascular events, ECG adverse events, and any temporally-related adverse event, defined as events which occur within 24 hours of BMN 190 infusion; any of these events must be reported to BPV using the appropriate eCRF, irrespective of severity, seriousness, or causality within 24 hours of a study site awareness. Device-related events (eg, infection, malfunction with an associated AE, such as leaking reservoir or a problem that ends the administration of study drug for that visit) require the completion of the Device Event Report Form in addition to eCRF reporting. All removed or replaced implantable ICV devices must be reported as device-related events and should 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.

Subjects will be monitored during and following infusion (Section 9.4.4). Any AE, including anaphylaxis and other hypersensitivity or allergic reaction, occurring within 24 hours after the start or restart of a BMN 190 infusion, regardless of investigator assessment of study drug relationship, will be assessed as a hypersensitivity reaction. As stated above, the investigator must report the event to BPV using the appropriate eCRF within 24 hours of a hypersensitivity reaction. The investigator is encouraged to discuss with the BioMarin medical monitor all AEOSIs as defined above.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.2 Diagnosis versus Signs and Symptoms

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

10.4.3 Adverse Events Occurring Secondary to Other Events

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

10.4.4 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 (such as seizures). Each recurrence of the AE should be recorded on the AE eCRF.

10.4.5 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** 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 is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of study drug, more frequent follow-up assessments, further diagnostic investigation, etc.)

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

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

10.4.6 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. Ongoing AEs from Study 190-201 will be recorded as medical history in Study 190-202 on the appropriate eCRF.

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

10.4.7 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition (refer to Section 9.7.6.2). 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.

10.4.8 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 10.2).

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 (excludes prophylactic ICV replacement)
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Receive scheduled therapy (study drug or otherwise) for the study indication

10.4.9 Deaths

All deaths that occur during the AE reporting period (refer to Section 10.1), regardless of attribution, will be recorded on the AE eCRF and expeditiously reported to the Sponsor (in compliance with applicable regulations) as an SAE. If the death is assessed as related the device (or any of its components), the study specific Device Report Form must be completed and submitted to BPV within 24 hours of the site becoming aware of the event.

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” on the eCRF. If the death is attributed to progression of the disease or condition being studies, record “Disease Progression” as the SAE term on the eCRF.

10.4.10 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 10.1 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.

10.4.11 Reporting Requirements

10.4.11.1 Expedited Reporting Requirements

All SAEs AEOSIs, and pregnancies that occur during the course of the AE Reporting Period, whether or not considered related to study drug, must be reported via eCRF to 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 is assessed as related to the device (or any of its components), 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).

10.5 Urgent Safety Measures

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

IRB/EC/REB is notified at the same time." The 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 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 (i.e., 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.

10.6 BioMarin Pharmacovigilance Contact Information

Contact information for BioMarin Pharmacovigilance is as follows:

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

The investigator is encouraged to discuss with the BioMarin medical monitor any AE for which the issue of seriousness is unclear or questioned. The investigator is also encouraged to discuss with the BioMarin medical monitor all events of special interest referenced in Section 10.3. Contact information is as follows:

Name: Temitayo Ajayi
Address: 105 Digital Drive
Novato, CA 94949 USA
Phone: (415) 382-5084
E-mail: temitayo.ajayi@bmrn.com

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 modified Hamburg Scale scores, and MRI data, which has 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 30patients 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).

BioMarin plans to construct a combined database with demographics, genotype, CLN2 disease rating scale scores, and supporting clinical data from both natural history studies. MRI imaging data may be included, if feasible. Patients will have scores for the Weill Cornell Scale, the Hamburg Scale, or both scales. BioMarin will investigate the feasibility of imputing both CLN2 disease scores for all patients using clinical data to derive the missing domains. At minimum, there are two shared domains in the two CLN2 disease scales (gait/motor and language), which might be combined.

The natural history data will be used to (1) better understand the performance properties of the two CLN2 disease scales, (2) evaluate correlations between the scales and independent clinical measures, (3) identify other potential clinical outcomes that are relevant and change with disease duration and severity, and (4) generate the group of untreated patients that will be used for comparison to the treated study population of Study 190-201 and Study 190-202.

11.2 Disease-Specific Rating Scales

Disease severity has been evaluated by two CLN2 disease-specific rating scales: the Hamburg Scale (Steinfeld, 2002); (Worgall, 2008) and the Weill Cornell Scale (Dyke, 2012);

(Worgall, 2007). Both consist 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 four domain scores for a final rating of 0 (severely impaired) to 12 (normal).

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 each rating scale will be completed (Appendix 1), the 2 domains common to both, motor (Hamburg) or gait (Weill Cornell) and language, are expected to be most useful for this study. The remaining 2 domains in each rating scale (Appendix 1) are less likely to be informative for this study. In the Hamburg Scale, vision and seizure domains are weak indicators of disease severity since (1) ICV-delivered BMN 190 is not expected to penetrate the posterior ocular chamber to reach the optic nerve, and (2) seizures managed with pharmacotherapy preclude measurable change in response to treatment, respectively. Similarly, in the Weill Cornell Scale, feeding and myoclonus domains are not ideal for this study since (1) the feeding score may be misleading since a feeding tube often is inserted merely to facilitate care and, thus, does not reflect disease severity necessarily, and (2) the myoclonus score may be misleading since presence or absence of different movement disorders (chorea, tremor, athetosis) are presumed to reflect disease severity.

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 at least two registries (Weill Cornell Medical Center in New York and University Medical Center in Hamburg, Germany).

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. Magnetic resonance spectroscopy (MRS) in patients with CLN2 disease has demonstrated reduced neuronal N-acetyl-aspartate (NAA), reduced NAA/creatine metabolite

ratios, and increased myoinositol/creatine rations 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 (Katz, 2014). Therefore, this first clinical study of CLN2 disease will include MRI measurement of ventricular volume.

12 STUDY PROCEDURES

12.1 Screening/Baseline

Baseline values will be recorded at first infusion, Week 1 Day 1 of Study BMN 190-202. These values will serve as the Baseline values for Study 190-202.

A 2-week Screening period will occur beginning with the Week 47 visit of Study 190-201. During this period, 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.

The following procedures will be performed during the Screening Period:

- Informed consent/assent
- Criteria for study entry
- Pregnancy testing

12.2 Treatment Visit(s)

12.2.1 Every Visit (every 2 weeks ± 3 days)

Treatment visits should occur every 2 weeks (± 3 days) during the study. Every effort should be made to ensure that treatment visits occur on a fixed schedule every 2 weeks starting from the first treatment visit in the study.

The first treatment visit will occur at Week 1 of Study 190-202. During every visit, the following procedures will be performed:

- Medical history (Week 1 only)
- Vital signs (SBP, DBP, heart rate, oral body temperature, and respiration rate)
- For at least one infusion of BMN 190 (and preferably the next 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. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG.
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) 30 (±5) minutes after infusion end for 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) (not required for Week 1, as will be done at the Study Completion visit in Study 190-201)
- Assessment of device patency and device site infection
- Brief physical examination (not required for Week 1, as a complete physical examination will be done at the Study Completion visit in Study 190-201)
- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern) (not required for Week 1, as will be done at the Study Completion visit in Study 190-201)
- Concomitant medication assessment (not required for Week 1, as will be done at the Study Completion visit in Study 190-201)
- Study drug infusion
- Telephone call to parent/guardian approximately 48 hours after having been discharged from the visit

12.2.2 Every 8 Weeks

Every 8 weeks (± 3 days) (Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185, 193, 201, 209, 217, 225, 233), the following procedures will be performed:

- CLN2 disease rating scales

12.2.3 Every 12 Weeks

Every 12 weeks (± 3 days) (Weeks 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, 229), the following procedures will be performed:

- CSF/serum for immunogenicity
- 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.
- Blood/urine for clinical lab tests
- Neurological examination

12.2.4 Every 24 Weeks

Every 24 weeks (± 3 days) (Weeks 25, 49, 73, 97, 121, 145, 169, 193, 217), the following procedures will be performed:

- Height and body weight assessment
- CLN2 disease rating scales with videotaping
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) 30 (±5) minutes after infusion end
- EEG, standard awake
- MRI (±4-week window is allowed for this assessment and may be performed at the same time as a scheduled infusion)
- CSF/blood for disease-related biomarkers
- Optical coherence tomography
- CLN2-specific QoL questionnaire
- PedsQL
- Denver II Developmental Scale

12.2.5 Every 48 Weeks

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

- Complete physical examination

12.3 Study Completion or Early Termination Visit

The Study Completion visit will occur 2 weeks (± 3 days) after the last dose of BMN 190 (Week 239), or within 1 week of early study termination. At the Study Completion or Early Termination visit, the following procedures will be completed:

- Hamburg and Weill Cornell CLN2 disease rating scales (Appendix 1) videotaped
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities)
- EEG (standard awake)
- MRI (±4-week window is allowed for this assessment and may be performed at the same time as a scheduled infusion)
- CSF surveillance (cell count, protein, glucose, and culture)
- CSF and blood for biomarker assays

- CSF and serum for immunogenicity (TAb; NAb if TAb positive)
- 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)
- PedsQL
- 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.
- Optical coherence tomography
- CLN2-specific QoL questionnaire
- Denver II Developmental scale
- Neurological examination
- AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern)
- Concomitant medication assessment

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.

12.4 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:

- CLN2 disease rating scales (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.)
- Neurological examination
- Serum for immunogenicity (TAb)
- Serum for total IgE, C4, and tryptase
- Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- AE assessment (investigator may collect additional blood samples or CSF by lumbar puncture 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

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.).

12.5 Safety Follow-Up

Subjects will return to the study site 6 months after the last study treatment, when the following procedures will be completed:

- CLN2 disease rating scales (videotaping not required)
- ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities)
- EEG (standard awake)
- Serum for immunogenicity (TAb)
- Serum for total IgE, C4, and tryptase
- 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.
- Concomitant medication assessment

The 6-month Safety Follow-Up Visit will be waived for subjects who receive study drug in another BioMarin-sponsored study or registry within this 6-month period.

12.6 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.

13 DATA QUALITY ASSURANCE

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

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

The designated clinical data management group will enter or transfer eCRF 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 and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis and will be finalized prior to database lock. Unless otherwise stated, all analyses will be performed using SAS®.

14.1.1 Interim Analyses

Accruing study data will be summarized periodically for review by BioMarin. All summaries will be descriptive. Early stopping will be considered on the basis of safety only and will be based on clinical judgment; no inferential stopping rules will be employed.

14.2 Primary Efficacy Analysis

Because practical and ethical concerns preclude contemporaneous or untreated control subjects, CLN2 disease motor and language rating scale scores will be compared with historical data from existing CLN2 disease registries, as specified in the SAP.

14.3 Secondary Efficacy Analysis

The following parameters will be evaluated using descriptive statistics as outlined in the SAP:

- Various representations of brain volumes, as determined by MRI, will be summarized.

14.4 Exploratory Analyses

The following parameters will be evaluated, as specified in the SAP:

- Quality of life questionnaires
- Relationships among safety, immunogenicity and efficacy
- Denver II Developmental scale
- CSF/ blood biomarkers
- EEG, standard awake
- Preferential Looking Test; Optional Lea Vision Test or E Hook (or Tumbling E) Vision Test

- Optical coherence tomography

14.5 Immunogenicity Analysis

Immunogenicity tests will be performed using validated immunogenicity assays on serum and CSF samples. Samples of CSF and serum will be collected for anti-BMN 190 TAb and NAb testing, as detailed in **Error! Reference source not found.**. Collection must precede study drug infusion when collected for routine immunogenicity assessments. Baseline blood (serum) samples will be collected at the Study Completion visit in Study 190-201 to obtain a baseline TAb and NAb, every 12 weeks thereafter (Q12W), at the Study Completion or Early Termination visit, at the Device Safety Follow-Up visit, and at the Safety Follow-Up visit. CSF samples will be collected for anti-BMN 190 TAb and NAb testing at the Study Completion visit in Study 190-201 and every 12 weeks thereafter (Q12W). Serum and CSF NAb will be tested at Study Completion Visit in Study 190-201 and at subsequent time points when serum and CSF TAb are positive, respectively. No CSF immunogenicity assessments will be performed at either of the safety follow-up visits.

Incidence and titer summary statistics will be provided for serum and CSF TAb and 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 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). Potential associations between IgE positivity and hypersensitivity adverse events will be analyzed.

14.6 Safety Analysis

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 eCRF. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment, and severity for each dosing group.

Concomitant medications will be coded using World Health Organization Drug 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.

Results from continuous ECG monitoring (3- or 5-lead) and serial 12-lead ECGs will be descriptively summarized in terms of overall interpretation and abnormal findings. ECGs (12-lead) will be summarized in terms of investigator overall interpretation, abnormal findings, and quantitative intervals (QTcF, etc.).

14.7 Determination of Sample Size

The sample size will be determined by the number of subjects who complete Study 190-201 and decide to roll into Study 190-202. Up to 23 subjects are projected to enroll into Study 190-202.

14.8 Changes in the Conduct of the Study or Planned Analyses

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

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

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

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

15 DATA MONITORING COMMITTEE

No Data Monitoring Committee will be used for this study.

16 COMPENSATION, INSURANCE AND INDEMNITY

There will be no monetary compensation provided to subjects for their participation in this study. BioMarin is responsible for all study participation expenses, including tests, procedures, and treatments. In addition, BioMarin may reimburse the cost of travel for study-related visits after 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. eCRFs must be completed using a validated web-based application. Study site personnel or designee will be trained to enter the clinical data onto the eCRFs from source documentation using the web-based application. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable.

The investigator must review and electronically sign the completed eCRF casebook to verify its accuracy.

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 US 21 CFR Part 11, the web-based eCRF 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 policy is that study data on the eCRFs must be verifiable to 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 legally authorized representative) must also allow access to their medical records. Subjects will be informed of the necessity for such access and will confirm their agreement with this when providing informed consent. If an investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an “interview” style of data verification.

A BioMarin CRA (or designee) will compare eCRFs with original source documents at the study site and evaluate eCRFs for completeness and accuracy before designating them as “source data verified.” 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. Study 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 eCRF casebook can be locked, data fields must be source data verified and all queries closed. Refer to the Study Monitoring Plan for details on which fields must be

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

18 STUDY MONITORING AND AUDITING

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

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

21 REFERENCES

Arkin, LM, Sondhi, D, Worgall, S, Suh, LH et al. Confronting the issues of therapeutic misconception, enrollment decisions, and personal motives in genetic medicine-based clinical research studies for fatal disorders. Hum Gene Ther 16[9], 1028-1036. 2005.

Awano, T, Katz, ML, O'Brien, DP, Sohar, I et al. A frame shift mutation in canine TPP1 (the ortholog of human CLN2) in a juvenile Dachshund with neuronal ceroid lipofuscinosis. Mol Genet Metab 89[3], 254-260. 2006.

Brooks, R. EuroQol: the current state of play. Health Policy 37[1], 53-72. 1996.

Chang, M. CLN2. The Neuronal Ceroid Lipofuscinoses. New York: Oxford Univ Press, 2011: 80-109.

Crystal, RG, Sondhi, D, Hackett, NR, Kaminsky, SM et al. Clinical protocol. Administration of a replication-deficient adeno-associated virus gene transfer vector expressing the human CLN2 cDNA to the brain of children with late infantile neuronal ceroid lipofuscinosis. Hum Gene Ther 15[11], 1131-1154. 2004.

Dierenfeld, AD, McEntee, MF, Vogler, CA, Vite, CH et al. Replacing the enzyme alpha-L-iduronidase at birth ameliorates symptoms in the brain and periphery of dogs with mucopolysaccharidosis type I. Sci Transl Med 2[60], 60ra89. 2010.

Dyke, JP, Sondhi, D, Voss, HU, Shungu, DC et al. Assessment of Disease Severity in Late Infantile Neuronal Ceroid Lipofuscinosis Using Multiparametric MR Imaging. AJNR Am J Neuroradiol. 2012.

Giedd, JN, Snell, JW, Lange, N, Rajapakse, JC et al. Quantitative magnetic resonance imaging of human brain development: ages 4-18. Cereb Cortex 6[4], 551-560. 1996.

Karavelis A, Foroglou G, Selviaridis P et al. Intraventricular administration of morphine for control for intractable cancer pain in 90 patients. Neurosurgery 39[1], 57-62. 1996.

Katz ML, Coates JR, Sibigtroth CM, Taylor JD et al. Enzyme replacement therapy attenuates disease progression in a canine model of late-infantile neuronal ceroid lipofuscinosis (CLN2 disease). J Neurosci Res 92[11], 1591-1598. 2014.

Kronenberg MF, Laimer I, Rifici C et al. Epileptic seizure associated with intracerebroventricular and intrathecal morphine bolus. Pain 75[2], 383-387. 1998.

Kurachi, Y, Oka, A, Mizuguchi, M, Ohkoshi, Y et al. Rapid immunologic diagnosis of classic late infantile neuronal ceroid lipofuscinosis. Neurology 54[8], 1676-1680. 2000.

Lishner M, Perrin RG, Feld R et al. Complications Associated with Ommaya Reservoirs in Patients with Cancer: The Princess Margaret Hospital Experience and a Review of the Literature. Arch Intern Med 150[1], 173-176. 1990.

Msall, M. Measuring Functional Skills in Preschool Children at Risk for Neurodevelopmental Disabilities. Ment. Retard. Dev. Disabil. Res. Rev. 11, 263-273. 2005.

Seitz, D, Grodd, W, Schwab, A, Seeger, U et al. MR imaging and localized proton MR spectroscopy in late infantile neuronal ceroid lipofuscinosis. AJNR Am J Neuroradiol 19[7], 1373-1377. 1998.

Sleat, DE, El-Banna, M, Sohar, I, Kim, KH et al. Residual levels of tripeptidyl-peptidase I activity dramatically ameliorate disease in late-infantile neuronal ceroid lipofuscinosis. Mol Genet Metab. 2008.

Sleat, DE, Wiseman, JA, El-Banna, M, Kim, KH et al. A mouse model of classical late-infantile neuronal ceroid lipofuscinosis based on targeted disruption of the CLN2 gene results in a loss of tripeptidyl-peptidase I activity and progressive neurodegeneration. J Neurosci 24[41], 9117-9126. 2004.

Schulz, A, Ajayi, T, Specchio, N, de Los Reyes, E, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. N Engl J Med 2018; 378[20]:1898-1907.

Steinfeld, R, Heim, P, von Gregory, H, Meyer, K et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet 112[4], 347-354. 2002.

The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16[3], 199-208. 1990.

Vuillemenot, BR, Katz, ML, Coates, JR, Kennedy, D et al. Intrathecal tripeptidyl-peptidase 1 reduces lysosomal storage in a canine model of late infantile neuronal ceroid lipofuscinosis. Mol Genet Metab 104[3], 325-337. 2011.

Vuillemenot, BR, Kennedy, D, Reed, RP, Boyd, RB, et al. Recombinant human tripeptidyl peptidase-1 infusion to the monkey CNS: safety, pharmacokinetics, and distribution. Toxicol Appl Pharmacol 277[1], 49-57. 2014.

Worgall, S, Kekatpure, MV, Heier, L, Ballon, D et al. Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. Neurology 69[6], 521-535. 2007.

Worgall, S, Sondhi, D, Hackett, NR, Kosofsky, B et al. Treatment of late infantile neuronal ceroid lipofuscinosis by CNS administration of a serotype 2 adeno-associated virus expressing CLN2 cDNA. Hum Gene Ther 19[5], 463-474. 2008.

Xu, S, Wang, L, El-Banna, M, Sohar, I et al. Large-volume intrathecal enzyme delivery increases survival of a mouse model of late infantile neuronal ceroid lipofuscinosis. Mol Ther 19[10], 1842-1848. 2011.

22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Subjects

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

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

23 SIGNATURE PAGE

Protocol Title: A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease

Protocol Number: 190-202

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

Investigator Signature Date

Printed name: _____

Accepted for the Sponsor:

Medical Monitor Signature Date

Printed name: Temitayo Ajayi, MD

Sr. Medical Director, Rare Disease

24 APPENDICES

Appendix 1: Adapted CLN2 Disease Rating Scale

Hamburg LINCL Scale (Steinfeld, 2002), adapted for multicenter use			**Weill Cornell LINCL Scale** (Dyke, 2012b), 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

Hamburg LINCL Scale (Steinfeld, 2002), adapted for multicenter use			**Weill Cornell LINCL Scale** (Dyke, 2012b), adapted for multicenter use		
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 summary of significant protocol revisions; 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.

Section	Revision	Rationale for Change
Synopsis/Study Design 9.1/ Study Design and Plan	Patients will complete safety and efficacy assessments including CSF surveillance labs every 2 weeks, CLN2 disease scales every 8 weeks, ~~and physical examination,~~ clinical laboratory assessments, visual acuity tests, and immunogenicity tests every 12 weeks. MRI ~~MRI will be performed every 24 weeks. In addition~~, quality of life measures, OCT, EEG, developmental milestones (Denver II), ~~will be completed,~~ and blood and CSF samples for evaluating disease-related biomarkers will be collected every 24 weeks. Complete physical examination will be performed every 48 weeks.	3, 6, 8
Synopsis/Criteria for Evaluation	Safety: • electrocardiogram (ECG), 3- or 5-lead, 12-lead • ~~EEG, standard awake~~ • immunogenicity, includes anti-BMN 190 total antibodies (TAb) and neutralizing antibodies (Nab) in CSF; ~~and~~ TAb, NAb, ~~and TAb titers and~~ total IgE, and drug-specific IgE ~~positivity~~ in serum Efficacy: • CLN2 disease rating scales with videotaping • Total cortical grey matter volume • Quality of Life surveys • Developmental assessments ~~(exploratory)~~ • Disease-related biomarkers ~~(exploratory)~~ • EEG, standard awake • Assessments of visual acuity • Optical coherence tomography • ~~Neurological Exam~~	1, 3, 6

Section	Revision	Rationale for Change
	Immunogenicity: ~~anti-BMN 190 total antibodies (~~TAb~~)~~ and ~~neutralizing antibodies (N~~A~~ab~~)~~** in CSF**; ~~and~~ TAb**, NAb, total IgE, and drug-specific ~~and anti-BMN 190~~ IgE in serum.	
Synopsis/ Statistical Methods	Safety assessments include adverse events, clinical laboratory results, vital signs, ECGs, ~~EEGs,~~ and immunogenicity. Efficacy data include CLN2 assessments and MRI measurements of brain volumes.	3
6/ Investigators and Study Administrative Structure	Assessment of immunogenicity and disease-related biomarkers will be conducted by BioMarin. Clinical laboratory evaluations will be performed by local study site laboratories. Central laboratories will be used to evaluate TPP1 enzyme activity**,** magnetic resonance imaging (MRI) scans, and electroencephalograms (EEGs). Additional details will be provided in the corresponding Study Laboratory Manual.	3, 4
7.2/ Previous Clinical Studies	BMN 190 has been studied in human ~~The only previous~~ clinical trials 190-~~experience with this investigational product is the BMN 190-~~201 and 190-202. Study 190-201 was ~~trial,~~ 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. ~~. This study enrolled 24 subjects at least 3 years of age (mean 4.3 years, range 3-8 years) with a two-domain CLN2 disease score of 3- 6 on motor and language domains of the Hamburg Scale (mean total score 3.7, SD=0.95), with a score of at least 1 in each of these two domains. Fifteen subjects (63%) were female and 9 (38%) subjects were male. These subjects were enrolled in 3 cohorts which received escalating doses of BMN 190 and a final cohort who received stable dose of drug. The first 3-subject cohort received 30 mg qow infusions, the second 3-subject cohort received 100 mg qow infusions and the third 4-subject cohort received 300 mg infusions of BMN 190. A final 14-subject cohort received a stable dose of 300 mg of BMN 190 during their participation in the study. A single patient withdrew consent from the study (subject 1287-1007) after ICV reservoir placement and a single infusion because of inability to comply with study procedures. Therefore, the efficacy population comprised 23 of the 24 subjects enrolled into Study 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.	12

Section	Revision	Rationale for Change
	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, N Engl J Med). 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.	

Section	Revision	Rationale for Change
	~~All doses of BMN 190 administered were generally well tolerated and there were no early terminations due to adverse events in this study. The occurrence and severity of adverse events, particularly those related to hypersensitivity, did not appear to be associated with higher doses of BMN 190. 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.~~	
7.4/ Summary of Risks and Benefits	Nonclinical toxicity ~~No findings in any of the six nonclinical studies~~ have not identified drug ~~indicate adverse BMN 190~~-related adverse effects associated ~~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.~~ ~~Although a stand-alone CNS safety pharmacology study was not conducted, monthly neurologic and clinical examinations of dachshunds administered BMN 190 (4 or 16 mg) for 9 months in a repeated-infusion study revealed no clinical CNS signs in dachshunds attributable to BMN 190. CNS signs known from historical control data to be due to disease progression in this model (ataxia, tremor, myoclonus, proprioceptive deficits, and visual decline) were observed in treated and untreated TPP1-null dachshunds (Awano, 2006, Mol.Genet.Metab), (Katz, 2014, J.Neurosci.Res.). Furthermore, onset of disease-related neurologic signs was delayed 3.5 to 11 weeks following 4 mg BMN 190 and 10 to 28 weeks following 16 mg BMN 190, compared~~ with chronic ~~vehicle-treated controls.~~ ~~Given the lack of BMN 190-related safety concerns of these studies, the specific mechanism of BMN 190 action, and that nearly all (~99%) BMN 190 remains in the CNS after~~ ICV administration of BMN 190 to healthy or CLN2 animal models disease~~, untoward systemic safety effects are unlikely in human~~. 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. . ~~Furthermore, efficacy analysis of Study 190-201 showed an~~	12

Section	Revision	Rationale for Change
	~~attenuation of the decline in motor-language scores on the Hamburg CLN2 clinical rating scale, which when matched to members of the Hamburg natural history cohort by baseline score, age and genotype showed significant treatment benefit for BMN 190. Of the 24 patients enrolled into Study190-201, all but 2 patients 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 each year (0 to 6 point scale). Treatment during this stage protected further decline in the disease.~~ 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 ~~of possible efficacy~~, the overall risks and benefits support this protocol.	
7.4.2/ Risk of ICV Devices and Drug Administration	New text: 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.	9
Table 9.1.1/SOE	Changes to the SOE table and footnotes have been made to be consistent with changes made elsewhere in the protocol.	
9.3.3.1/ Stopping Criteria	Subjects with a score of 0 on the combined motor and language components of the Hamburg CLN2 rating scale at two consecutive visits ~~without any change~~ will be ~~removed~~ discontinued from treatment ~~the study~~.	10
9.3.5/ Duration of Subject Participation	A Safety Follow-Up visit will be conducted 6 months after the final BMN 190 infusion. The Safety Follow-Up visit will be waived for subjects who receive study drug in another BioMarin-sponsored study or registry within this 6-month period (refer to Section 10.1 and Section 10.2 for AE and SAE reporting instructions). For subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week device safety follow-up visit 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.	2

Section	Revision	Rationale for Change
9.4.4.1/ Safety Monitoring 9.7.5.2/ Device Malfunction 10.3/ Adverse Events of Special Interest 12.3/ Study Completion or 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,~~defined in the protocol)~~ should also be returned.	11
9.4.7/ Blinding	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.	3, 4
9.7 /Efficacy and Safety Variables	Although this study is designed to assess safety and tolerability primarily, efficacy will be assessed by impact on disease-specific clinical rating scales. ~~Secondary variables include~~ MRI is being assessed as a secondary efficacy variable. ~~and effect~~ Effect on quality of life (QoL), developmental milestones,~~).~~ Disease-related biomarkers, EEG, visual acuity, and optical coherence tomography (OCT) ~~and developmental milestones~~ will also be explored.	3, 6
9.7.3.1/ Quality of Life Testing	Quality of life will be assessed using 2~~3~~ different instruments: the PedsQL™ Measurement Model for Pediatric Quality of Life Inventory (PedsQL~~)), the EuroQol Health Status EQ-5D-5L Instrument,~~ and the CLN2-specific questionnaire.	7
9.7.2.2.2/ EuroQol Health Status EQ-5D-5L Instrument	~~The EQ-5D-5L instrument is a self-reported questionnaire designed to measure general health status (The EuroQol Group, 1990, Health Policy), (Brooks, 1996, Health Policy). The EQ-5D-5L is composed of 2 parts: a descriptive system that assesses 5 levels of perceived problems (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in 5 dimensions and the EQ visual analogue scale (EQ-VAS) assessment for overall health.~~	7

Section	Revision	Rationale for Change
9.7.3.4/ Electroencephalogram	**Moved:** A standard awake EEG will be recorded within 2 days before each infusion as indicated in Table 9.1.1. 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 Week 1 and as an AE thereafter. Evaluation will be done both locally and by a centralized vendor.	3, 4
9.7.3.5/ 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	6

Section	Revision	Rationale for Change
	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.	
9.7.3.6/ 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.	6
9.7.4/Immunogenicity	Immunogenicity tests will be performed using validated immunogenicity assays on serum and CSF samples. ~~Samples of blood (serum) will be collected for anti-BMN 190 TAb testing, and~~ **S**amples of CSF and serum will be collected for anti-BMN 190 TAb and NAb testing, as detailed in Table 9.1.1. Collection must precede study drug infusion when collected for routine immunogenicity assessments. Baseline blood (serum) samples will be collected at the Study Completion visit in Study 190-201 to obtain a baseline TAb and NAb, every 12 weeks thereafter (Q12W), at the Study Completion or Early Termination visit, at the Device Safety Follow-Up visit, and at the Safety Follow-Up visit. CSF samples will be collected for anti-BMN 190 TAb and NAb testing at the Study Completion visit in Study 190-201 and every 12 weeks thereafter (Q12W). Serum and CSF NAb ~~samples~~ will be tested at Study Completion Visit in Study 190-201 and at subsequent time points~~only~~ when serum and~~the corresponding~~ CSF TAb are~~sample~~	1

Section	Revision	Rationale for Change
	~~tests~~ positive, respectively.~~.~~ No CSF immunogenicity assessments will be performed at either of the safety follow-up visits.	
9.7.6.2/ Physical Examination	A complete physical examination will be performed as indicated in Table 9.1.1. A complete examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems (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).~~), and body weight and height.~~ Results of the neurologic examination may also be used to assess the efficacy of BMN 190. A brief physical examination will be performed otherwise, as indicated in Table 9.1.1. A brief examination will include general appearance, cardiovascular, respiratory, neurologic, and gastrointestinal assessments. Body weight and height assessments should be performed 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 revise 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	8, 9, 11

Section	Revision	Rationale for Change
	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, ~~defined in the protocol)~~ should also be returned.	
10.1/Adverse Events	All AEs/ SAEs/ adverse events of special interest (AEOSIs) / pregnancies will be recorded starting after the first dose of study drug in Study 190-202. Reporting of AEs/SAEs / AEOSIs/ pregnancies will continue until 6 months after either the last administration of study drug or the Early Termination visit. 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 follow-up visit 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 components required for infusion (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 device AE/SAE eCRF and the device report form and reported to BioMarin Pharmacovigilance (BPV) within 24 hours by entering the event information via EDC and completing the study specific device report form(s). Prophylactic replacement of the ICV must be reported as a device related event. The reporting period for device-related events is the same as the reporting period for all AEs and SAEs; if the device is removed prior to the 6 month safety follow-up visit, the follow-up safety reporting period for device-related events is 4 weeks from the removal of the device.	2, 9
10.2/ Serious Adverse Events	The reporting period for SAEs begins after the first dose of study drug in Study 190-202 and continues until 6 months after either the last administration of study drug or the Early Termination visit. 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. Refer to Section 10.1 for additional information regarding SAE reporting for these subjects. For subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week device	2

Section	Revision	Rationale for Change
	safety follow-up visit 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. If a subject is discontinued from the study prematurely, SAEs will be recorded at the Early Termination visit.	
10.4.8/ Hospitalization, Prolonged Hospitalization, or Surgery	• Perform a protocol-mandated procedure (excludes prophylactic ICV replacement)	9
12.1/ Screening/ Baseline	The following procedures will be performed during the Screening Period: • Informed consent/assent • Criteria for study entry • Pregnancy testing ~~• EQ-5D-5L~~	7
12.2.3/ Every 12 Weeks	Every 12 weeks (± 3 days) (Weeks 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181, 193, 205, 217, 229), the following procedures will be performed: • CSF/serum for immunogenicity ~~• Complete physical examination~~ • Visual acuity testing o 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.	6

Section	Revision	Rationale for Change
12.2.4/ Every 24 Weeks	Every 24 weeks (± 3 days) (Weeks 25, 49, 73, 97, 121, 145, 169, 193, 217), the following procedures will be performed: • Height and body weight assessment • CLN2 disease rating scales with videotaping • ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) 30 (±5) minutes after infusion end • EEG, standard awake • MRI (±4-week window is allowed for this assessment and may be performed at the same time as a scheduled infusion) • CSF/ blood for disease-related biomarkers • Optical coherence tomography • CLN2-specific QoL questionnaire • PedsQL • ~~EQ-5D-5L~~ • Denver II Developmental Scale	6, 7, 8
12.2.5/ Every 48 Weeks	The following procedures should be performed every 48 weeks during the study: • Complete physical examination	8

Section	Revision	Rationale for Change
12.3/ Study Completion or Early Termination Visit	The Study Completion visit will occur 2 weeks (± 3 days) after the last dose of BMN 190 (Week 239), or within 1 week of early study termination. At the Study Completion or Early Termination visit, the following procedures will be completed: • Hamburg and Weill Cornell CLN2 disease rating scales (Appendix 1) videotaped • ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) • EEG (standard awake) • MRI (±4-week window is allowed for this assessment and may be performed at the same time as a scheduled infusion) • CSF surveillance (cell count, protein, glucose, and culture) • CSF and blood for biomarker assays • CSF and serum for immunogenicity (TAb; NAb if TAb positive) • Vital signs (SBP, DBP, heart rate, oral body temperature, and respiration rate) • Complete physical examination, including neurologic examination • Height~~, including neurological examination~~ and body weight assessment • Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis) • PedsQL • Visual acuity testing ○ All subjects will undergo Preferential Looking Testing. In addition, for those children who retain the cognitive function tneo adhere to testing, the Lea Vision Test or E Hook (or Tumbling E) Vision Test should also be performed during the same assessment. • Optical coherence tomography • ~~EQ-5D-5L~~	6, 7, 8, 13

Section	Revision	Rationale for Change
	• CLN2-specific QoL questionnaire • Denver II Developmental scale • Neurological examination • AE assessment (investigator may collect additional blood samples for safety or immunogenicity testing for any AE of concern) • Concomitant medication assessment	
12.4/ Device Safety Follow-Up Visit	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: • <u>CLN2 disease rating scales (videotaping not required)</u> • 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.) • Neurological examination • Serum for immunogenicity (TAb) • Serum for total IgE, C4, and tryptase • Routine clinical laboratory tests (hematology, blood chemistry, and urinalysis) • AE assessment (investigator may collect additional blood samples or CSF by lumbar puncture for safety or immunogenicity testing for any AE of concern<u>), including ongoing events at the time of the last dose or new events related to study drug.</u> • Concomitant medication assessment	2, 5

Section	Revision	Rationale for Change
12.5/ Safety Follow-Up	Subjects will return to the study site 6 months after the last study treatment, when the following procedures will be completed: • CLN2 disease rating scales (videotaping not required) • ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) • EEG (standard awake) • Serum for immunogenicity (TAb) • Serum for total IgE, C4, and tryptase • 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. • Concomitant medication assessment	2, 5, 8
14.4/ Exploratory Analyses	The following parameters will be evaluated, as specified in the SAP: • Quality of life questionnaires • Relationships among safety, immunogenicity and efficacy • Denver II Developmental scale • CSF/ blood biomarkers	3, 6, 13

Section	Revision	Rationale for Change
	• EEG, standard awake • Preferential Looking Test; Optional Lea Vision Test or E Hook (or Tumbling E) Vision Test • Optical coherence tomography	
14.5/ Immunogenicity Analysis	Immunogenicity tests will be performed using validated immunogenicity assays on serum and CSF samples. Samples of CSF and serum will be collected for anti-BMN 190 TAb and NAb testing, as detailed in Table 9.1.1. Collection must precede study drug infusion when collected for routine immunogenicity assessments. Baseline blood (serum) samples will be collected at the Study Completion visit in Study 190-201 to obtain a baseline TAb and NAb, every 12 weeks thereafter (Q12W), at the Study Completion or Early Termination visit, at the Device Safety Follow-Up visit, and at the Safety Follow-Up visit. CSF samples will be collected for anti-BMN 190 TAb and NAb testing at the Study Completion visit in Study 190-201 and every 12 weeks thereafter (Q12W). Serum and CSF NAb will be tested at Study Completion Visit in Study 190-201 and at subsequent time points when serum and CSF TAb are positive, respectively. No CSF immunogenicity assessments will be performed at either of the safety follow-up visits. ~~Samples of blood (serum) will be collected for anti-BMN 190 TAb testing and samples of CSF will be collected for anti-BMN 190 TAb and NAb testing before the first infusion (i.e., at the completion of Study 190-201) and every 12 weeks thereafter or within one week of the Early Termination visit, CSF NAb samples collected prior to first infusion and will be tested at subsequent immunogenicity time points only when the CSF TAb is positive. Total IgE, C4, and tryptase samples will be collected prior to first infusion and within 1 hour of a hypersensitivity event. Collection must precede study drug infusion when collected for routine immunogenicity assessments.~~ Incidence and titer summary statistics will be provided for serum ~~TAb, CSF TAb,~~ and CSF TAb and 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.	1

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Final Statistical Analysis Plan

Study BMN 190-202

A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease

10 March 2021

1 APPROVALS

Title: A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease

Protocol: 190-202

Date: 10 March 2021

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LIST OF APPENDICES

2 SUMMARY OF CHANGES

Study 202 is a study of extended treatment in patients who completed Study 201. Analyses and reporting have combined the data of Study 201 and Study 202 and have followed the SAP of Study 201. The final CSR for Study 202 will be based on combined data of Study 201 and Study 202 and will follow a new SAP with rationale given below.

Study 201 Version 2: The statistical analysis plan (SAP) for Study 201 was amended so that the population for the primary analysis of the primary endpoint was closer to ITT and consistent with the population for the primary analysis of the primary endpoint outlined in the integrated summary of efficacy (ISE). The original SAP required that the primary analysis include only subjects who have a CLN2 score between 3 and 6 inclusive just prior to initiation of 300 mg dosing, with a score of at least 1 in each of the two domains.
This requirement, an inclusion criteria for the study, was no longer a requirement for the primary analysis but was retained as a sensitivity analysis of the primary endpoint.

Study 201 Version 3: After discussions with regulatory agencies, the SAP was amended to place the responder analysis as the primary endpoint. The analysis of slopes remains an important endpoint and was performed as well. The primary analysis for each endpoint was based on the ITT population. Analyses were also performed after removing patients who entered the study with a CLN2 score of 6 that did not drop below 6 during follow-up.

The primary endpoint was defined as the absence of an unreversed 2-point decline or score of zero in CLN2 score by Week 48 (Study Day 340 relative to first 300 mg infusion).
An unreversed 2-point decline was clarified as “any decline of 2-points or more that had not reverted to a 1-point decline (or better) as of the last recorded observation”.

Study 202 Version 1: The Study 202 SAP is initiated as a revision of the Study 201 Version 3 SAP. The key change is that the primary endpoint of unreversed ML 2-point decline or score of zero has been revised (1) to evaluate over the full duration of follow-up instead of the initial 48 weeks of Study 201 (2) to compare against patient data from a natural history database (Study 901; two sample analysis) instead of against a fixed response rate of 50% (one sample analysis). The method of analysis for the primary endpoint is the Kaplan-Meier method and Cox proportional hazards model with covariate adjustment.
The rationale for this change is that with extended follow-up the focus of evaluation is long term and not the first 48 weeks on treatment. With longer-term and variable follow-up, patients will have variable follow-up (censoring) and the Cox model allows for evaluation of response rates with censoring. The Cox model also allows comparison to a natural history

cohort (Study 901) since it is unclear what response rate is an appropriate fixed-point comparison for a one sample analysis.

Study 202 Version 2: The Study 202 SAP is amended to include a survival analysis as an exploratory endpoint.

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical (classification system)
CLN2	late-infantile neuronal ceroid lipofuscinosis disease, also known as classical late-infantile CLN2, cLINCL, or Jansky-Bielschowsky disease, a form of Batten Disease
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	electrocardiogram
EEG	electroencephalogram
HAE	hypersensitivity adverse event
HLGT	high-level group term
HRQL	health-related quality of life
ICV	intracerebroventricular,intracranial volume
IgE	immunoglobulin E
ITT	intent-to-treat
L	language subscale of the CLN2 disease rating scale
M	motor subscale of the CLN2 disease rating scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
mg	milligram
ML	Combined score of motor and language subscales on the CLN2 disease rating scale
MLV	Combined score of motor, language, vision subscales on the CLN2 disease rating scale
MLVS	Combined score of motor, language, vision, seizure subscales on the CLN2 disease rating scale
MRI	magnetic resonance imaging
NAb	neutralizing anti-TPP1 antibody
OCT	optical coherence tomography
PedsQL	measurement model for Pediatric Quality of Life Inventory
PLT	preferential looking test
PT	preferred term
QOL	quality-of-life

Abbreviation	Definition
qow	every other week
S	seizure subscale of the CLN2 disease rating scale
PT	preferred term (MedDRA or WHO drug)
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	Standardized MedDRA Query
SOC	system organ class (MedDRA)
TAb	total anti-TPP1 antibody
TEAE	treatment-emergent adverse event
TRE	temporally-related event
WBV	whole brain volume
WHO	World Health Organization

4 INTRODUCTION

Study 190-202 is an extension of parent Study 190-201. It is a multi-center, multinational, extension study to evaluate BMN 190 treatment in patients with CLN2 who completed 190-201 (Study 201). All patients who have completed 48 weeks in Study 201 were eligible to enroll in Study 901-202 (Study 202).

The purpose of this Statistical Analysis Plan (SAP) is to present a description of the planned analyses for safety and efficacy data in Study 202. However, in order to characterize the safety and efficacy of longer-term treatment with BMN 190, Study 201 will be combined with the Study 202 to support analyses, i.e. data from Study 201 through study completion/ database lock will be pooled into Study 202. Furthermore, efficacy endpoint of CLN2 scores from the combined study (Study 201/202, treated subjects) will be compared with the Study 901 natural history controls (untreated subjects, herein Study 901).

For a detailed analysis plan for Study 201, please refer to Study 201 SAP version 3 dated on 25 March 2016.

Protocol history for Study 202 is as follows:

- Original protocol (3 October 2014)
- Amendment 1 (12 August 2015)
- Amendment 2 (16 November 2015)
- Amendment 3 (26 February 2016)
- Amendment 4 (17 March 2017)
- Amendment 5 (05 May 2017)
- Amendment 6 (17 December 2018)

The first subject was consented on 13 September 2013 for Study 201. The first subject enrolled in Study 202 on 02 February 2015.

4.1 Objectives of Study

The primary objectives of this study include the following:

- To evaluate the long-term safety of BMN 190 administration at 300 mg qow in patients with CLN2.
- To assess change in motor and language (ML) subscales of the CLN2 disease rating scale in patients with CLN2 receiving BMN 190 at 300 mg qow.

Secondary objectives of this study include the following:

- To assess changes in quantitative assessment of magnetic resonance imaging (MRI).
- To assess change in CLN2 disease scale total score.
- To evaluate quality of life (QoL) with long-term BMN 190 administration.

Exploratory objectives of this study include the following:

- To evaluate age-appropriate developmental milestones with long-term BMN 190 administration.
- To evaluate the impact of treatment on disease-related biomarkers from cerebrospinal fluid (CSF) and blood.

4.2 Study Design

This is a Phase 1/2, open-label, multi-center, multinational, extension study to evaluate the safety and efficacy of BMN 190 treatment in subjects with CLN2 who completed Study 201. All subjects who completed 48 weeks of BMN 190 treatment in Study 201 were eligible to enroll in Study 202.

The Screening period for Study 202 started simultaneously with the Week 47 visit in Study 201. Baseline values for Study 202 were recorded on the day of the first infusion (Week 1, Day 1) of Study 202, for all subjects on active treatment. The first dose of BMN 190 in Study 202 (Week 1/Study Day 1) was given following the Week 49 study assessments in Study 201. This study was open label, with all subjects continuing on treatment with BMN 190 300 mg qow.

4.3 Study Population

All patients who complete 48 weeks in the 201 study may be eligible to enroll in Study 202.

4.3.1 Key Inclusion Criteria

The key inclusion criterion is: Must have completed 48 weeks in Study 201.

4.3.2 Key Exclusion Criteria

If any of the following exclusion criteria apply, a patient will not be eligible to participate in the study:

- Has had a loss of 3 or more points in the combined motor and language components of the Hamburg CLN2 rating scale between Baseline of Study 201 and the Study Completion visit in Study 201 and would not benefit from enrolling in the study in the Investigator's discretion.

- Has a score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale.

4.4 Study Dosage and Administration

All study subjects will be administered BMN 190 300 mg by intracerebroventricular (ICV) infusion every other week.

4.5 Sample Size Determination

The sample size will be determined by the number of subjects who complete Study 201 and decide to roll into Study 202. Twenty-three subjects enrolled into Study 202.

4.6 Blinding and Randomization Methods

This is an open-label, non-randomized study.

4.7 Interim Analysis

Accruing study data will be summarized periodically for joint review by BioMarin and the Data Monitoring Committee (DMC). All summaries will be descriptive. Early stopping will be considered on the basis of safety only and will be based on clinical judgment; no inferential stopping rules will be employed.

Interim analyses of safety and efficacy were performed in September 2014 and January 2015 with plans to file data early to regulatory authorities if compelling efficacy were observed.

Interim analyses of safety and efficacy were performed based on data cut-off dates of:

15 October 2015: interim CSR for Biologics License Application

3 June 2016: 120 Safety Update

01 November 2016: interim CSR update for drug application

5 GENERAL ANALYSIS CONSIDERATIONS

Analyses will be conducted based on the combined data of Study 201 and Study 202 (Study 201/202). Efficacy analyses of CLN2 rating scales will also include comparison with a natural history database (Study 901), based on matching.

5.1 Analysis Populations

5.1.1 Efficacy

5.1.1.1 Intent-to-treat Analysis Population

The intent-to-treat (ITT) analysis population comprises all subjects from Study 201/202 who received any amount of study drug and report any efficacy results but excluding one subject (1287-1007) who terminated from the Study 201 after a single infusion of study drug due to unwillingness to continue with study procedures.

5.1.1.2 Study 901 Intent-to-treat Analysis Population

The Study 901 ITT population comprises the Study 901 subjects who satisfy the Study 201 inclusion criterion: Age ≥ 3, and at least one ML score ≥3 at age ≥3 years.

5.1.1.3 Study 901 Evaluable Population

The evaluable population will include Study 901 subjects in ITT population who have at least two CLN2 assessments with values within the range 1 - 5 and at least 6 months apart.

5.1.2 Safety Analysis Population

The Safety analysis population will comprise all subjects in Study 201/202 who had an ICV reservoir implanted in Study 201.

5.2 Treatment Group Presentation

Study 201/202 subjects will be pooled into a single group for the efficacy and safety analyses. Analyses that compare CLN2 scores for Study 201/202 subjects to Study 901 natural history controls will be presented as two groups and include the Study 201/202 ITT patients and Study 901 evaluable patients.

5.3 Pooling of Data from Sites with Small Enrollment

Given the small sample size of this study, subjects will be pooled across all sites for the primary efficacy and safety analyses.

Results may be examined within site on an exploratory basis.

5.4 Study Day Derivation

For dates on or after initiation of study drug, "Study Day" is defined as follows:

- Study Day = [Date – (date of first study drug)] + 1

For dates preceding initiation of study drug, "Study Day" is defined as follows:

- Study Day = [Date – (date of first study drug)]

Thus the day of first study drug is Study Day 1, and the day preceding first study drug is Study Day -1. There is no Study Day "0".

Date of first study drug is the first dosing date in Study 201.

For Study 901, the time of events is presented in terms of the subjects' age, in units of months. The Study 901 assessment that is used as a match to a Study 202/202 subject will be assigned as Study Day 1. Study Day is assigned to subsequent records assuming 30-day months, e.g., Study Day 31, 61, 91, etc.

5.5 Definition of Baseline

The definition of baseline will depend on context. The following general principles will apply:

- For evaluation of safety that includes the safety of the ICV reservoir, baseline will be the last observation preceding ICV implantation, if available. If no such pre-implantation observation exists, baseline will be the first value following ICV implantation, assuming that this is clinically reasonable.
- For evaluation of safety that is focused on the safety of BMN 190, baseline will be the last observation preceding the first infusion of BMN 190.
- For evaluation of efficacy of the 300 mg dose of BMN 190 with respect to CLN2 ratings and MRI measurements, baseline will be the last observation preceding the first 300 mg infusion.
- For evaluation of efficacy of the 300 mg dose of BMN 190 with respect to quality-of-life assessments (the disease-based QOL and the two PedsQL assessments) and developmental milestones (Denver II), baseline will, in general be the last observation preceding the first infusion of BMN 190.
- For the assessments conducted in Study 202 only (e.g. visual acuity testing, optical coherence tomography, electrocardiogram (ECG; 3- or 5-Lead.), neurological examination, hypersensitivity labs, ED-5D-5L QoL instrument etc), baseline will be the first available assessment in the 202 study.

For analyses of CLN2 scales based on matching, the baseline for subjects in Study 901 is taken as the assessment at the age (in months) for the match.

5.6 Visit Windows for Analysis

Patient visits for assessment of CLN2 scales and MRI is synchronized to a schedule relative to the first dose of 300 mg. CLN2 scales and MRI data will be windowed according to the schedule (see Appendix 1). For CLN2 scales in Study 201, the visit window defined for the 300 mg dose will be utilized (see Study 201 SAP dated on 25 March 2016).

Other efficacy and safety assessments are not synchronized and windowing will not be used.

5.7 Handling of Dropouts and Missing Data

Missing or partial dates will be examined within their context. Full dates will be imputed conservatively, with consideration given to the domain and context. For example, AE dates will be imputed so as to ensure that an AE is considered treatment emergent and has the longest possible duration, assuming these are ambiguous with the missing/partial date.

For the primary efficacy analysis (responder) of CLN2 ratings, missing data will be handled by the Kaplan-Meier and Cox proportional hazards model methods. For the analysis of slopes, missing data is not expected to be an issue since the analysis is based on estimated slopes using baseline and last assessment.

A linear imputation algorithm is used for some of the analyses that compare Study 201/202 with Study 901. The CLN2 assessment schedule for Study 901 is not regular and does not generally correspond to CLN2 assessment frequency in Study 201/202. Summaries of CLN2 score using a window grid would have highly variable N which is difficult to interpret. For this reason, interpolation will be used. Summaries of Study 201/202 and Study 901 CLN2 score data will be based on data that has been imputed to the Study 201/202 visit target, using linear interpolation between Study 901 subject visits. Details are provided in Appendix 2.

Additional analyses will be conducted as appropriate to evaluate the impact of the COVID-19 pandemic on the study conduct and results, especially for the treatment effect as estimated in the trial.

6 SUBJECT DISPOSITION

The following will be summarized:

- the number of subjects enrolled
- the number of subjects who did not fulfill all inclusion/exclusion criteria
- the number of subjects who received study drug
- reason for termination from study
- length of time on Study 201/202

7 DISCONTINUATION AND COMPLETION

This is addressed in Section 6, Subject Disposition.

8 PROTOCOL DEVIATIONS

The number of subjects with protocol deviations in Study 201/202 will be summarized with respect to deviation class (major or minor) and deviation category (e.g., out of window, procedure not done etc.)

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic variables (age, sex, ethnicity, and race), height, and weight will be descriptively summarized.

Baseline disease characteristics (e.g., age at diagnosis, genotype, and CLN2 scores at screening and prior to initiation of study drug) will be descriptively summarized.

10 MEDICAL HISTORY

Medical history will be coded in accordance with the most current version of MedDRA at the time of coding.

Medical history will be summarized by system organ class (SOC) and preferred term (PT).

11 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

Prior and concomitant medications in Study 201/202 will be defined as follows:

- A “prior” medication is any medication that was taken prior to the initiation of study drug in Study 201, regardless of dose level of study drug.
- A “concomitant” medication is any medication that was taken on or after the initiation of study drug in Study 201, regardless of the dose level of study drug. This can occur in two ways:
    - The medication was initiated on or after the initiation of study drug.
    - The dosing of a prior medication extended into the study drug dosing period. If the stop date of a prior medication is reported as “continuing”, the prior medication will be assumed to be a concomitant medication as well.

Prior and concomitant medications will be mapped in accordance with the most current version of World Health Organization (WHO) Drug at the time of coding.

Prior and concomitant medications will be summarized separately, in terms of the number of subjects taking medications within each Anatomical-Therapeutic-Chemical class (ATC) and preferred term medication.

12 COMPLIANCE

The total amount of study drug (in mg) will be calculated as defined in the next section (Section 13, Extent of Exposure to Study Drug).

Measures of compliance will include:

- Actual study drug intake relative to planned study drug intake, expressed as a proportion:

$$100\% \times \frac{\text{Actual intake (mg)}}{\text{Planned intake (mg)}}$$

- Number (%) of missed infusions

These measures will be described descriptively over (1) the entire study period in Study 201/202 and (2) the 300 mg dosing period in Study 201/202.

13 EXTENT OF EXPOSURE TO STUDY DRUG

Exposure to study drug in Study 201/202 will be descriptively summarized in terms of the following:

- Total number of infusions, regardless of dose level
- Number of infusions at each dose level
- Total duration of dosing, regardless of dose level (time from first infusion to last infusion, in weeks)
- Duration of dosing at 300 mg (time from first 300 mg infusion to last infusion, in weeks)
- Total exposure over all infusions, regardless of dose level (in mg)
- Total exposure to 300 mg (in mg)

Exposure (mg) should be calculated as follows:

Exposure (mg) = [Volume (mL)] × [Study drug concentration (mg/mL)]

- If "volume" is explicitly recorded on the CRF, then use the recorded volume.
  If "volume" is NOT recorded on the CRF, and if "entire volume infused" is indicated, then assume the volume is 10 mL, as specified by protocol.
- "Study drug concentration" is determined from the "Dose" that is recorded on CRF page 18. Dose should be 30, 100, or 300 mg. (If otherwise, then flag.) We will assume that the concentration of prepared study drug for the three dose levels is as follows:

Dose	Concentration
30 mg	3 mg/mL
100 mg	10 mg/mL
300 mg	30 mg/mL

(Reference: Pharmacy Manual v2 10-Oct-2013)

If there are multiple records for a given infusion, e.g., then "exposure" is calculated separately for each record, and exposures are then summed across records.

14 EFFICACY EVALUATIONS

Study 201/202 efficacy will be evaluated from the first dose of 300 mg. Efficacy variables will be summarized by visit unless otherwise specified. For the CLN2 disease rating scales, comparison of Study 201/202 will be made with natural history data (Study 901).

For CLN2 scales, two sets of analyses comparing the Study 201/202 patients to Study 901 will be considered. The first set will compare the Study 201/202 ITT population and the Study 901 evaluable population. The second set will be based on 1-1 matching between the Study 201/202 ITT population and Study 901 evaluable cohort. The matched analyses will be based on a single matched set and the algorithm for 1-1 matching is described in Appendix 3. The matching criteria are:

- Equal baseline ML score
- Baseline age within 3 months
- Genome: equal number of common alleles (c.622C→T, c.509.1G→C)

We refer to the two sets of analyses as the full and matched sets. All analyses of CLN2 scales will use the full set and key analyses of CLN2 scales will also use the matched set as specified below.

14.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the time to unreversed ML 2-point decline or score of zero.

14.1.1 Primary Analysis Method

Time to unreversed ML two-point decline or score of zero will be analyzed using the Kaplan-Meier method and the Cox proportional hazards model. The Cox model will include baseline ML score and baseline age as continuous covariates and genome (common alleles) and sex as categorical covariates. The analyses will be performed on the full and matched sets.

14.1.2 Supportive Analysis

14.1.2.1 Time to Unreversed ML Score of Zero

Time to unreversed ML score of zero will be analyzed similarly as the time to unreversed ML 2-point decline or score of zero (Section 14.1.1).

14.1.2.2 Rate of decline

An important measure of treatment effect is the rate of decline in the 0-6 point ML score, scaled to a 48-week time period. Since the endpoint is a rate of decline, as opposed to a rate

of change, it is generally expected to be a positive number, with larger values representing a steeper deterioration of clinical status over time. The rate of decline will be estimated for each subject. Estimation of rate of decline is described in Appendix 4.

The mean rate of decline in Study 201/202 subjects will be compared to the mean rate of decline in Study 901 subjects using a 2-sample t-test. The null and alternative hypotheses to be tested are:

H_0: $\mu_{201/202} = \mu_{901}$

H_1: $\mu_{201/202} \neq \mu_{901}$

where $\mu_{201/202}$ represents the treated population mean rate of decline from the Study 201/202 and μ_{901} represents the untreated population mean rate of decline from Study 901. Treatment effect will be estimated as the difference in the mean of the slopes: Study 901 versus Study 201/202 subjects. Testing will use the two-sample t-test at significance level of α=0.05. The analyses will be produced for the full and matched sets.

An additional analysis of covariance (ANCOVA) model will be run for the full set. The model will include baseline ML score and baseline age as continuous covariates, genome (number of common alleles) and sex as a categorical covariate. Least square means and 95% CI for treatment versus natural history will be provided.

An additional mixed effects model for repeated measures (MMRM) will be run for the full set. Slope on treatment versus untreated will be estimated and tested using a random slope and intercept model. The model will include baseline ML score and baseline age as continuous covariates, genome (number of common alleles) and sex as a categorical covariate.

14.1.2.3 Motor (M) Scale

Time to unreversed motor 2-point decline or score of zero in Motor scale will be analyzed using the Kaplan-Meier method and the Cox proportional hazards model similarly as the primary endpoint (see Section 14.1.1).

The mean rate of decline of M scale in Study 201/202 subjects will be compared to the mean rate of decline in Study 901 subjects using a 2-sample t-test as described in Section 14.1.2.2.

The analyses will be performed on the full set only.

14.1.2.4 Language (L) Scale

Language (L) scale will be analyzed similarly to Motor (M) scale (Section 14.1.2.3).

14.1.2.5 Descriptive Summaries

For comparative summary of CLN2 scores, additional many-to-one matching between the Study 901 evaluable population and Study 201/202 ITT population will be conducted using criteria described in Appendix 3a.

Summary by Visit

To enable a descriptive assessment of CLN2 scores at common time points in which all subjects contribute to the descriptive statistics, each subject of Study 201/202 and Study 901 will have their CLN2 scores imputed to those time points using linear interpolation (see Section 5.7). The time points for interpolation will be in accord with the Study 201/202 schedule of CLN2 assessments.

Summary statistics of interpolated values and change from baseline by visit will be produced. A graph of mean change from baseline and standard error by visit will be produced. These analyses will be produced for the individual CLN2 scale domains motor (M), language (L), vision (V), seizure (S), and the composites ML, MLV, MLVS. The analyses will be produced for the full and matched sets (1-1 and many-to-one).

Summary statistics will also be produced for non-interpolated 201/202 data using the full set.

Individual Subject Plots

Data of each of the Study 201/202 subjects will be plotted with the matched Study 901 subject's data based on 1-1 and many-to-one matching.

14.2 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints will be analyzed for Study 201/202 using the ITT population.

14.2.1 MRI parameters

The key secondary endpoint, in concept, is brain atrophy. This will be evaluated with one or more of the following MRI measurements:

- Whole brain volume (WBV) (in mm^3)
- Volume of cerebrospinal fluid (in mm^3 and as a percentage of WBV)
- Volume of total cortical gray matter (in mm^3 and as a percentage of WBV)
- Total white matter volume (in mm^3 and as a percentage of WBV)
- Whole brain apparent diffusion coefficient (mm^2/s)

Values and change from baseline will be described descriptively over time.

14.3 Exploratory Endpoints

Exploratory endpoints will be analyzed using the ITT population.

14.3.1 Survival

Time to death will be analyzed using the Kaplan-Meier method and the Cox proportional hazards model. The analyses will be performed on the full and matched sets. For the analysis based on the matched set, survival will be measured from time of baseline to time of death (event) or time of last CLN2 assessment (censored). The Cox model will include baseline ML score and baseline age as continuous covariates and genome (common alleles) and sex as categorical covariates. For the analysis based on the full set, survival will be measured from birth to time of death (event) or time of last CLN2 assessment (censored). The Cox model will include genome (common alleles) and sex as categorical covariates.

14.3.2 CSF/Plasma Biomarkers

Analysis of disease-related biomarkers from CSF and blood will be conducted if usable biomarkers have been identified.

14.3.3 Developmental Milestones

Achievement of developmental milestones is assessed by the Denver II Development Scale for Study 201 and the Denver II Development Scale Updated for Study 202.

The Denver II Development Scale includes domain of Language and Gross Motor. Overall test interpretation is provided. Each domain includes the number of cautions and number of delays. The updated version in Study 202 includes domain of Personal Social, Fine Motor Adaptive, Language and Gross Motor. Each domain includes the number of passes, number of fails, number of cautions, number of delays and developmental age of most advanced pass. Overall test interpretation is provided as well.

The overall interpretation of the test – normal, suspect, or untestable – will be summarized at scheduled assessment times will be summarized for Study 201 and 202 separately.
For assessments done by Denver II Development Scale Updated, age equivalent performance (month) on personal social, fine motor adaptive, language and gross motor will be plotted over time using the age at assessment (month) for each subject. Age equivalence and change from baseline will be summarized. The ratio of change in age equivalence and change in age will be summarized at each visit as well as the last visit.

14.3.4 Anti-epileptic treatment

Graphical displays for each patient will include start and end dates for anti-epileptic treatment, with indication whether prophylactic or acute use. Convulsion adverse events (AEs) per SMQ and the 0-3 point S score will also be plotted on the patient chart.

14.3.5 Quality of Life

Quality of life is assessed with the following survey instruments:

14.3.5.1 PedsQL - Parent Report for Toddlers

This will be summarized as described in the PedsQL documentation, "Scaling and scoring of the Pediatric Quality of Life Inventory PedsQL". The following text briefly summarizes the scoring of the Parent Report for Toddlers:

The Parent Report for Toddlers is composed of 21 items comprising 4 dimensions:

- Physical Functioning (8 items)
- Emotional Functioning (5 items)
- Social Functioning (5 items)
- School Functioning (3 items)

Each item is scored on a 5-point Likert scale from 0 (Never) to 4 (Almost always).

The scoring procedure is a follows: Items are reverse-scored and transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

Score by dimension: If more than 50% of the items in the scale are missing, the scale scores should not be computed. The mean score = Sum of the items over the numbers of items answered.

Psychosocial Health Summary Score: This is the sum of the items over the number of items answered in the Emotional, Social, and School Functioning scales.

Total Score: This is the sum of all the items over the number of items answered on all the scales.

The various scores (by dimension, psychosocial health summary, and total scores) and change from baseline will be descriptively summarized.

14.3.5.2 PedsQL - Parent Family Impact

This will be summarized as described in the PedsQL documentation, "Scaling and scoring of the Pediatric Quality of Life Inventory PedsQL." The following text briefly summarizes the scoring of the Parent Report for Toddlers:

The full PedsQL Family Impact Module is composed of 36 items comprising 8 dimensions. In Study 201, BioMarin is collecting 5 of the 8 dimensions:

- Physical Functioning (6 items)
- Emotional Functioning (5 items)
- Social Functioning (4 items)
- Cognitive Functioning (5 items)
- Communication (3 items)

Each item is scored on a 5-point Likert scale from 0 (Never) to 4 (Almost always).

The scoring procedure is as follows: Items are reverse-scored and transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

Score by dimension: If more than 50% of the items in the scale are missing, the scale scores should not be computed. The mean score = Sum of the items over the numbers of items answered.

Parent HRQL Summary score (20 items): This is the sum of the items over the number of items answered in the Physical, Emotional, Social, and Cognitive scales.

(Modified) Total Score: This is the sum of all the items over the number of items answered on all the scales.

The various scores (by dimension, Parent HRQL, and the (modified) total scores) and change from baseline will be descriptively summarized.

14.3.5.3 CLN2 Disease-based Quality of Life

This instrument was developed by BioMarin, modeled upon the PedsQL instruments, and will be summarized similarly to the PedsQL instruments, as described below.

The CLN2 Disease-based QOL instrument is composed of 28 items comprising 6 dimensions:

- Seizures (6 items)
- Feeding / No G-tube (4 items)
- Feeding / with G-tube (3 items)
- Sleep (5 items)
- Behavior (6 items)
- Daily activities (4 items)

Each item is scored on a 5-point Likert scale from 0 (Never) to 4 (Almost always).

The scoring procedure is a follows: Items are reverse-scored and transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

Score by dimension: If more than 50% of the items in the scale are missing, the scale scores should not be computed. The mean score = Sum of the items over the numbers of items answered.

Total Score: This is the sum of all the items over the number of items answered on all the scales.

The scores (by dimension, and total) and change from baseline will be descriptively summarized.

14.3.6 Retinal Anatomy using Optical Coherence Tomography (OCT)

The retinal thickness parameters were assessed by Optical coherence tomography (OCT) for each eye in Study 202:

- Central Foveal
- Central Retinal
- Retinal – 3mm nasal to the fovea
- Retinal – 3mm temporal to the fovea

The overall OCT assessment (normal, abnormal) was collected for each eye as well. OCT results will be provided in a listing.

14.3.7 Visual Acuity

All subjects undergo Preferential Looking Testing (PLT). 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 are also performed during the same assessment.

The assessment of visual acuity was only conducted in Study 202. The results will be provided in a listing.

14.3.8 EQ-5D-5L

The EQ-5D-5L instrument is a self-reported questionnaire designed to measure general health status (The EuroQol Group, 1990, Health Policy), (Brooks, 1996, Health Policy). The EQ-5D-5L is composed of 2 parts: a descriptive system that assesses 5 levels of perceived problems (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in 5 dimensions and the EQ visual analogue scale (EQ VAS) assessment for overall health.

The assessment of EQ-5D-5L was conducted in Study 202 but was discontinued with the implementation of protocol amendment 6 (dated on 17 December 2018). The data collected in database will be provided in a listing.

14.3.9 Electroencephalograms (EEG)

Electroencephalograms (EEG) will be summarized in terms of the proportion of subjects with epileptiform activity and/or frequency slowing, in combination with the activity's location (focal vs. generalized), at baseline and at any time after initiation of study drug.
The proportion of subjects showing new such activity (defined by the combination of activity and location) relative to baseline will be summarized. EEG evaluations from local and central vendor will be analyzed separately.

14.4 Examination of Efficacy by Subgroup

The impact of genotype, with a focus on the c.622C>T and c.509-1G>C mutations, on outcome may be examined.

Demographic characteristics, investigative site, or geographical region may be examined.

Various sub-intervals of the treatment period may be examined, e.g., the entire dosing experience, experience after initiation of 300 mg dosing, experience after entering Study 202.

All subgroup analyses are exploratory.

15 SAFETY EVALUATIONS

Safety will be assessed by examination of adverse events (including serious adverse events [SAEs], hypersensitivity adverse events (HAEs), infusion-associated reactions, and adverse events of special interest), clinical laboratory results (including chemistry, hematology, urinalysis, and CSF), vital signs, ECGs, and immunogenicity.

The Safety analysis population is defined in Section 5.1.2.

Summarization of safety data will be descriptive. No formal inference will be conducted.

Unless stated otherwise, baseline is generally defined as the last measurement prior to initiation of study drug, regardless of dose level in Study 201. However, as warranted by context, some summaries will use a value recorded prior to implantation of the ICV reservoir as baseline.

15.1 Adverse Events

Adverse events will be coded in accordance with the most current version of MedDRA at the time of coding.

Only treatment-emergent adverse events (TEAEs) will be summarized. A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following ICV surgery. If the onset date of an AE is missing or indeterminate, the AE will be considered treatment-emergent.

15.1.1 All Adverse Events

Adverse events will be summarized in terms of incidence during the study period, by system organ class (SOC) and preferred term (PT).

Adverse events will be further summarized by severity (CTCAE grade). If a subject reports the same event more than once, with different severities, the greatest severity will be summarized.

The following subsets of adverse events will also be summarized:

- AEs scored by the investigator as “related” to study drug and/or study device
- AEs with outcome of death
- AEs that did not resolve, or that resolved with sequelae
- AEs resulting in termination from study and/or permanent discontinuation of study drug
- AEs resulting in dose reduction

15.1.2 Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be summarized in a similar manner to general adverse events. A listing of AEs for subjects who died and a listing of all SAEs will be provided.

15.1.3 Adverse Events Causing Premature Discontinuation

Adverse events that caused premature discontinuation of study or study drug will be listed.

15.1.4 Convulsion Events

Convulsion events are adverse events that map to the broad Convulsions Standardized MedDRA Query (SMQ). Convulsion events will be summarized by SOC, PT and severity. The convulsion events will also be summarized by 24 week study intervals: 0-24 weeks, 24-48 weeks, etc.

15.1.5 Hypersensitivity Adverse Events

A hypersensitivity adverse event (HAE) is defined as any adverse event that maps into either:

- the broad "hypersensitivity" Standardized MedDRA query (SMQ), or
- the broad algorithmic "anaphylactic reaction" SMQ

  Note: The algorithm requires either one or more of the following: an "A" event, or "B & C" events, or "B & D" events, or "C & D" events, with onset within 24 hours of start of a study drug infusion.

HAEs will be summarized in a similar manner to general adverse events.

15.1.6 Temporally-related events (TRE)

A temporally-related events (TRE) is defined as any adverse event with onset after initiation of a study drug infusion and within 24 hours of the start or restart of the infusion.

TREs will be summarized in a similar manner to general adverse events.

15.1.7 Adverse Events of Special Interest

"Adverse events of special interest" (AESIs) are defined in the study protocol amendment 6 (Section 10.3) to include:

- hypersensitivity adverse events (defined above)
- temporally-related events (defined above)
- status epilepticus
    - Status epilepticus is defined to comprise the following MedDRA preferred terms: petit mal epilepsy, status epilepticus.

- hydrocephalus (communicating and noncommunicating)
    - Hydrocephalus is defined to comprise the following MedDRA preferred terms: hydrocephalus, congenital hydrocephalus.
- meningitis
    - Meningitis is defined to comprise the MedDRA preferred terms presented in Appendix 5.
- unexpected rapid decline on CLN2 disease scale not attributable to other causes.
    - This will be identified by clinical review.
- 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.)
- Cardiac and ECG events
    - It is defined to comprise the preferred terms within the SOCs of vascular disorders and cardiac disorders, the High Level Term of ECG investigations, and the HLGT of cardiac and vascular investigations.

Adverse events of special interest will be summarized in a similar manner to general adverse events.

15.2 Clinical Laboratory Tests

Chemistry, hematology, and urinalysis will be summarized by presentation of summary statistics (e.g., means, medians, standard deviations, etc.) for baseline values, for values observed after initiation of study drug in Study 201 (e.g., within-subject medians, minima and maxima over the follow-up period), and changes from baseline in these values.

These labs will also be summarized in terms of results relative to lab reference ranges (within, below, or above reference range). The baseline distribution will be presented. The within-subject percentage of follow-up lab values that are above reference range will be summarized; one summary will include all study subjects regardless of baseline values; a second summary will exclude subjects whose baseline values are above reference range. Similarly, the within-subject percentage of follow-up labs that are below reference range will be summarized in a manner analogous to that described above.

Samples of standard clinical laboratory Cerebrospinal Fluid Surveillance (CSF) for routine surveillance (cell count with differential, protein, glucose, and culture) will be summarized in a similar manner to clinical lab tests.

15.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature) are recorded approximately every 2 weeks, prior to, during, and after each infusion of study drug. See the protocol Schedule of Events for the exact schedule.

Each vital sign will be summarized by presentation of summary statistics (e.g., means, medians, standard deviations, etc.) for baseline values, for values observed after initiation of study drug in Study 201 (e.g., within-subject medians, minima and maxima over the follow-up period), and changes from baseline in these values.

15.4 Height and Weight

Height and weight will be summarized in a similar manner as vital signs.

15.5 Physical Examinations

Clinically significant abnormalities observed during physical examinations are to be recorded under Medical History at Screening in Study 201 or as adverse events thereafter. Therefore, physical examinations will not be summarized but will be presented in listings only.

15.6 Electrocardiograms

Quantitative ECG (12-lead) parameters include heart rate, RR, PR, QRS and QT. ECG will be summarized by presentation of quantitative summary statistics (e.g., means, medians, etc.) for baseline values and values observed after initiation of study drug in Study 201 (e.g., within-subject medians, minima and maxima over the follow-up period) . Changes from baseline at these timepoints will be similarly summarized.

QTcF will be further summarized in terms of the number of subjects with observed values >450, >480, or >500 msec, or with changes from baseline >30 or >60 msec.

The number of subjects with one or more ECGs that are judged abnormal, and clinically significantly abnormal, will be summarized.

The continuous ECG monitoring (3- or 5-lead) were performed for all subjects for at least one infusion of BMN 190 (and preferably the next infusion) in Study 202, The ECG should begin 15 (± 5 minutes) prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG. The 3- or 5-lead ECG data in Study 202 will be provided in a listing. The overall interpretation from investigator ECGs will be cross tabulated using a shift table at baseline vs. the worst post-baseline results and the last visit.

15.7 Neurological Examination

The neurological examination was conducted every 12 weeks in Study 202. It includes mental status, speech language, cranial nerve examination, motor strength, motor tone, abnormal movements, reflexes, sensory, gait, romberg`s test, nystagmus and coordination. The neurological examination results (normal vs abnormal) will be listed only.

15.8 Immunogenicity

Immunogenicity tests will be performed using validated immunogenicity assays. Routine immunogenicity tests will include total antibody (TAb) and neutralizing antibody (NAb) in the CSF and serum. NAb testing will not be performed if the TAb is negative. A subset of serum and CSF NAb samples were tested to detect inhibition of cerliponase alfa enzyme activity. For all assays conducted, 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. Titer results will be presented in a cumulative manner to include 190-201 data and summarized by visit as well as by change at study timepoint from study baseline in 190-201. Potential impact of anti-drug antibodies (ADA) on efficacy and safety will be explored.

In the event of serious or severe (≥Grade 3) hypersensitivity AE, a 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 might be analyzed.

16 REFERENCES

Brooks, R. EuroQol: the current state of play. Health Policy 37[1], 53-72. 1996.

Denver II Training Manual, Denver Developmental materials, Inc., P.O. Box 371075, Denver, CO 80237-5075 (last copyright: 2009, Wilhelmine R. Frankenburg)

Outbound Data Delivery Specification; Document version: Draft_v0.1_02Apr2014; Protocol Identifier: 190-201. ICON Medical Imaging, 2800 Kelly Road, Suite 200, Warrington, PA.

Pharmacy Manual v2 10-Oct-2013, Clinical protocol number 190-201. BioMarin Pharmaceutical Inc.

The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16[3], 199-208. 1990.

17 APPENDICES

Appendix 1: Windows

Assessment	Derived Visit	Scheduled Visit Day [b]	Window (day)
CLN2 disease rating scales i=1,2…	Week 49 [a]	337	[-, 365]
	Week 49 + i*8	337 + i*56	[310+i*56, 365+i*56]
MRI i=1,2…	Week 9	57	[-, 113]
	Week 25	169	[114, 253]
	Week 49	337	[254, 421]
	Week 49 + i*24	337+i*168	[254+i*168, 421+i*168]

[a]: Week 49 starts at the first day in Study 202

[b]: It is the study day relative the first dose in Study 201

Appendix 2: Imputation of CLN2 Scores at Nominal Time points

To enable a descriptive assessment of CLN2 scores at common time points in which all subjects contribute to the descriptive statistics, each subject of the 201/202 and 901 studies will have their CLN2 scores imputed to those time points.

Nominal time points are Weeks 4, 8, 12, … 144, 168 with corresponding target Analysis Days 29, 57, 85, ... 1009, 1177.

The imputed CLN2 value at each target Analysis Day is calculated by linear interpolation. If a target Analysis Day is not bracketed on both sides by CLN2 scores, but there is a single CLN2 assessment within 28 days, inclusive, of the target Analysis Day, then that single assessment is used for imputation (observation carried forward). The imputed data of the 901 patients is truncated to have no longer follow-up than the corresponding imputed data for the Study 201/202 patient matched.

Appendix 3: Matching of Study 901 and Study 201/202 patients (1-1)

This matching algorithm is based on maximizing the number of Study 201/202 subjects matched to Study 901 subjects and satisfying several criteria (baseline ML score equal, genome: equal number of common alleles, baseline age close and no more than 3 months apart). The data of Study 901 subjects will be restricted and includes the assessment at the age of the match as the baseline assessment. Duration of follow-up is measured with respect to this baseline. Follow-up assessments up to the largest duration that is less than or equal to

the full follow-up duration of the matched 201/202 subject are included for the matched analysis. If this derived duration of follow-up for the Study 901 subject is not of duration 6 months or greater then matching at this age of assessment will not be considered.
For Study 901, where the first assessment of ML has the value 6, backwards imputation of the value 6 to earlier ages is allowed.

Distance is defined as the absolute value of the difference in baseline age for the potential match. Study 201/202 subjects are paired off from first through last. No Study 901 subject is matched more than once. To maximize the number of matched pairs, and overall low mean squared distance, at each pairing:

- Identify the Study 201/202 subject who has not yet been matched and has the least potential Study 901 candidates for pairing based on the requirement for equal baseline ML score, equal number of common alleles and distance ≤ 3. If greater than one Study 201/202 subject is identified, break the tie by considering the number of potential Study 901 candidates for matching based on the requirement of distance ≤ 2. Potentially there are still ties and repeat as needed using distance criteria based on thresholds ≤ 1 and ≤ 0.
- For the selected Study 201/202 subject, match with the Study 901 subject who has not yet been matched and has a (ML, age of assessment) combination that minimizes the distance measure. There may be greater than one Study 901 subject that satisfies minimal distance in which case choose the 901 Subject who has fewest potential Study 201/202 matches based on the distance ≤ 3 (and ≤ 2, ≤ 1, ≤ 0 as needed).
If there are no Study 901 subjects who satisfy distance ≤ 3 then there is no match for the Study 201/202 subject.
- It is possible that there remains greater than one 901 patients selected. In this situation, ties are broken down based on the following criteria ordered: exact genome, sex, seizure age, onset age, country.
- Repeat till all Study 201/202 subjects have been attempted for match. This completes the 1-1 matching.

Appendix 3a: Matching of Study 901 and Study 201/202 patients (many-one)

To facilitate comparison of Study subjects to Natural History subjects with respect to the clinical course over time, as represented by the 0- to 6-point CLN2 scores vs. time, Study 201/202 subjects will be matched to Study 901 Natural History subjects on the basis of study subjects' baseline CLN2 scores. Once the matches based on subject baseline CLN2 scores have been identified, more refined matching will be done by further matching on the basis of

(1) subject age at baseline and (2) genotype. That is, three sets of matching will be done, based on these matching criteria:

- Study subject's baseline CLN2 score
- Study subject's baseline CLN2 score and age at baseline
- Study subject's baseline CLN2 score and genotypic classification

The matching algorithms can result in zero, one, or multiple Study 901 Natural History matches for any given Study 201/202 subject.

Algorithm for matching on Study subject's baseline CLN2 score

For a given Study 201 subject, identify the baseline CLN2 score and analysis day.

Then identify each Study 901 subject who has one or more records with a CLN2 score equal to the given Study 201 subject's baseline CLN2 score. For each such Study 901 subject, determine the mid-point of these records that match Study 201 subject baseline score, and consider this to be the "baseline" record for this Study 901 subject when paired with this Study 201 subject. Assign an "analysis day" time value to this Study 901 baseline record that equals the Study 201 subject's baseline analysis day. Assign "analysis days" to subsequent Study 901 records relative to this pseudo-baseline record; use the convention that each "month" has 30 days.

Algorithm for further matching on Study subject's age at baseline

The algorithm is the same as matching on baseline CLN2 score alone , with the additional requirement that the age (in years) of the Study 901 subject's matched baseline is equal to the given Study 201 subject's age at enrollment.

Algorithm for further matching on Study subject's genotype

For purpose of matching on genotype, "genotype" will be defined as a trichotomous variable, based on the presence or absence of the two predominant mutations, c.622>T and c.509-1G>C, as follows:

- Both: Both alleles are predominant mutations – that is, two of one mutation, or one of each mutation
- One: Exactly one allele is a predominant mutation. The other allele is not a predominant mutation.
- None: Neither allele is a predominant mutation.

Note: We assume understanding is that the IVS5-1G>C mutation identified in the Study 901 dataset is the same as the c.509-1G>C mutation in the Study 201 database.

Similarly to matching on (baseline CLN2 score and) baseline age, to further match on Study subject's genotype, the algorithm starts with the matching obtained by matching on subjects' baseline CLN2 scores. For a given Study 201 subject, the Study 901 matches will be culled to retain only those Study 901 subjects whose genotypic classification is equal to the Study subject's genotypic classification.

Appendix 4: Estimation of Rate of decline

The purpose of this appendix is to describe the algorithm for estimation of rate of decline in study subjects.

General Algorithm

The rate of decline is calculated as follows:

1. Identify a starting point and an ending point, where a "point" is a bivariate observation comprised of (1) a CLN2 score and (2) a timepoint.
2. Determine the slope of the line connecting the two points:

$$\text{Slope} = \frac{(\text{Ending CLN2 score}) - (\text{Starting CLN2 score})}{(\text{Ending date}) - (\text{Starting date})}$$

3. Calculate the rate of decline as the negative of the line's slope, scaled to a 48-week time period:

$$\text{Rate of decline} = (-1) \times (48 \times 7) \times \text{Slope}$$

A General Consideration in Selecting the Starting Point

When a subject with a baseline CLN2 score <6 enrolls in the study, we assume that the subject enrolls at a random time point within the time period at which the subject "resides" at that value. This assumption has implications for the determination of the starting point for subjects with an initial CLN2 score of 6.

If the subject enrolling with CLN2 = 6 does not subsequently have a drop in CLN2 score, then the starting point is the baseline assessment. Otherwise we must wait until the subject's score drops to <6 before using the subject in analysis. If the subject has multiple records at that lower score, it would be inappropriate to select the earliest such observation, given the assumption in the previous paragraph. To consistently select the earliest (or last) observation could introduce bias, by systematically inflating (or decreasing) the time until a subsequent drop. To mitigate the introduction of bias in this situation, we therefore select the midpoint between the first and last of any multiple observations.

Estimation of Rate of Decline in Study Subjects

The starting assessment will be defined by the following algorithm:

- Identify the baseline CLN2 assessment appropriate for the given analysis.
- If the baseline CLN2 score is less than 6, then use this assessment; skip the next bullet.
- If the baseline CLN2 score is a 6:
    - If the subject did not have a decline in CLN2 score during follow-up then use this assessment.
    - If the subject drops below a 6, move forward in time to the earliest CLN2 rating that is less than or equal to 5. Determine the set of contiguous visits with this CLN2 score; this may be a single observation or multiple observations. Define the starting time as the mid-point between the first and last of these visits.

The ending assessment is the last observation with a CLN2 score greater than 0.

Once starting and ending points have been identified, calculate the rate of decline and scale it to 48 weeks as described above.

Appendix 5: MedDRA Preferred Terms Corresponding to Meningitis

The study protocol identifies "meningitis" as an adverse event of special interest (AESI). Meningitis is defined to comprise the MedDRA preferred terms presented below:

Central nervous system infection	Meningitis histoplasma
Meningitis	Meningitis leptospiral
Meningitis aseptic	Meningitis listeria
Meningitis aspergillus	Meningitis meningococcal
Meningitis bacterial	Meningitis mumps
Meningitis borrelia	Meningitis neonatal
Meningitis candida	Meningitis noninfective
Meningitis chemical	Meningitis pneumococcal
Meningitis coccidioides	Meningitis salmonella
Meningitis coxsackie viral	Meningitis staphylococcal

Meningitis cronobacter
Meningitis cryptococcal
Meningitis echo viral
Meningitis enterococcal
Meningitis enteroviral
Meningitis eosinophilic
Meningitis exserohilum
Meningitis fungal
Meningitis gonococcal
Meningitis haemophilus
Meningitis herpes
Meningitis streptococcal
Meningitis toxoplasmal
Meningitis trypanosomal
Meningitis tuberculous
Meningitis viral
Herpes zoster meningitis
Herpes simplex meningitis
Pachymeningitis
Propionibacterium acnes
Pseudomonas aeruginosa meningitis

Long-Term Open-Label Extension Study of Cerliponase Alfa in Children with CLN2 Disease: Safety and Efficacy After >5 Years of Therapy

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ABSTRACT

BACKGROUND: Cerliponase alfa is a recombinant human tripeptidyl peptidase 1 (TPP1) enzyme replacement therapy for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) caused by mutations in the *TPP1* gene. The aim of this study was to determine the long-term safety and efficacy of intracerebroventricular (ICV) cerliponase alfa in children with CLN2 disease.

METHODS: This analysis includes cumulative data from a 48-week primary study (NCT01907087) and a completed 240-week open-label extension with 6-month safety follow-up (NCT02485899), conducted at 5 hospitals in Germany, Italy, the UK, and the USA between 13 September 2013 and 10 December 2020. Children aged 3-16 years with CLN2 disease confirmed by genetic analysis and enzyme testing were eligible for inclusion. Historical untreated controls with CLN2 disease in the DEM-CHILD database were used as a comparator group. Treatment was ICV infusion of 300 mg cerliponase alfa every 2 weeks. The primary efficacy outcome was time to an unreversed 2-point decline or score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale.

FINDINGS: Twenty-four participants were enrolled in the primary study (15 female, 9 male); 23 participants enrolled in the extension and received 300 mg cerliponase alfa for a mean (range) of 272·1 (162·1–300·1) weeks: 17 participants completed the extension and 7 discontinued prematurely. Treated patients were significantly less likely than historical untreated controls to have an unreversed 2-point decline or score of 0 in the combined motor-language domains (hazard ratio, 0·14; 95% confidence interval, 0·06 to 0·33; $p<0·0001$). All participants experienced ≥1 adverse event (AE) and 21 (88%) experienced a serious AE; 9 participants experienced ICV device-related infections with 9 events in 6 participants resulting in device replacement. There were no study discontinuations because of an AE. There were no deaths and treated patients were significantly less likely to die than historical controls.

INTERPRETATION: Cerliponase alfa treatment over a period of >5 years was seen to confer a clinically meaningful slowing of motor and language function decline in children with CLN2 disease. Although our study is limited by the lack of a contemporaneous control group, the results provide critical insights into the outcomes of long-term treatment.

FUNDING: BioMarin Pharmaceutical Inc.

RESEARCH IN CONTEXT

Evidence before this study

We conducted a PubMed search for clinical trials published between 1 January 1966 and 24 May 2023, using the text word search terms “CLN2 disease,” “neuronal ceroid lipofuscinosis type 2,” or “Batten disease”, and “cerliponase alfa” without language restriction. To date, the safety, efficacy, and immunogenicity of cerliponase alfa have been assessed in a completed multicentre, single-arm, dose-escalation clinical study (NCT01907087, EudraCT 2012-005430-11) after all participants had received at least 48 weeks of 300 mg dosing and an interim analysis (an additional 48 weeks of data) of a 240-week extension study (NCT02485899, EudraCT 2014-003480-37). Compared with historical controls, patients treated with the recommended 300 mg cerliponase alfa every 2 weeks for at least 96 weeks experienced a statistically significant slowing of decline in motor and language function. Adverse events, including seizures, pyrexia, vomiting, device-related infections, and hypersensitivity reactions, were shown to be manageable and did not result in treatment discontinuation. These data represent a clinically meaningful preservation of motor and language function and an acceptable risk profile and have increasingly led to cerliponase alfa becoming the standard of care for children with CLN2 disease, where this treatment is available.

Added value of this study

This report presents final long-term outcomes (>5 years of treatment) based on cumulative data from the primary and extension studies of safety and efficacy of cerliponase alfa in children with CLN2 disease. Participants in the study ranged in age between 3.1 and 8.9 years at the time of enrolment. After >5 years of follow-up in the long-term extension study, all patients had reached the age at which disease progression would be expected to be very advanced, and thus the data presented here provide additional information about the efficacy of treatment through the expected phase of most rapid decline. Moreover, many patients had reached an age exceeding the typical life expectancy for untreated patients, and a significant impact of treatment on mortality was observed.

Implications of all the available evidence

Taken together, the data show that long-term intracerebroventricular administration of 300 mg cerliponase alfa every 2 weeks in children with CLN2 disease slows decline in critical motor and language functions compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these did not result in treatment discontinuation, and immunogenicity does not appear to be a limiting factor with respect to either safety or efficacy.

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) is a rare, rapidly progressive paediatric neurodegenerative disease caused by mutations in the tripeptidyl peptidase 1 *TPP1* gene resulting in TPP1 enzyme deficiency.[1,2] Deficient activity of TPP1 is associated with intracellular accumulation of lysosomal storage materials and neuronal cell death.[1] Children with CLN2 disease appear healthy at birth and often show delayed language acquisition before other symptoms manifest, typically at age 2-4 years with seizures and ataxia.[1,3,4] The classic late-infantile disease phenotype is characterized by loss of motor and language functions beginning at around 3 years of age and includes language regression and eventual complete loss of expressive language; new onset or worsening ataxia and complex movement disorders resulting in complete loss of independent mobility; worsening epilepsy, which may become intractable; progressive loss of ability to swallow; progressive dementia; deterioration of vision leading to blindness; and death by adolescence.[1,5,6]

In 2017, the European Medicines Agency and the United States Food and Drug Administration approved cerliponase alfa (Brineura; BioMarin Pharmaceutical Inc., Novato, CA) enzyme replacement therapy for treatment of CLN2 disease. Efficacy of cerliponase alfa was demonstrated by comparing changes in the combined motor and language domains of the CLN2 Clinical Rating Scale in treated patients with those in untreated historical controls enrolled in the DEM-CHILD NCL database.[7] Motor and language function are hallmarks of CLN2 disease severity and can be reliably measured by clinical raters: each domain of the CLN2 Clinical Rating Scale is scored from 0 to 3, with a score of 3 representing normal function and a score of 0 representing complete loss of function (Table S1). Compared with untreated historical controls, patients treated with 300 mg of cerliponase alfa for at least 96 weeks were shown to be less likely to experience an unreversed 2-point decline or score of 0 in the combined motor and language domains (hazard ratio [HR], 0·08; 95% confidence interval [CI], 0·02 to 0·23; $p<0·0001$) and had a lower mean rate of decline in motor and language function.[7] Common adverse events (AEs) in treated patients included seizures, pyrexia, vomiting, and hypersensitivity reactions.

We present cumulative data from the primary and completed open-label extension studies to assess the safety and efficacy of cerliponase alfa in children with CLN2 disease over >5 years of treatment.

METHODS

Study Design

Study 190-201 was a 48-week, single-arm, open-label, multicentre, dose-escalation study of intracerebroventricular (ICV) cerliponase alfa, conducted between September 2013 and November 2015 at 5 tertiary care hospitals (1 each in Germany, Italy, and the United States; and 2 in the United Kingdom).[7] Upon completion of the 48-week primary study, participants with a combined motor-language score of >0 on the CLN2 Clinical Rating Scale (Table S1) were eligible to enroll in study 190-202, an open-label extension study conducted between 02 February 2015 and 10 December 2020. Participants continued to receive 300 mg of ICV cerliponase alfa every 2 weeks for 240 weeks (Figure S1). A safety follow-up visit was performed 6 months after completion of the 240-week dosing period. Cumulative data from both the primary and extension studies are presented.

The primary and extension studies were registered at clinicaltrials.gov (NCT01907087 and NCT02485899) and EudraCT (2012-005430-11 and 2014-003480-37). See the Supplementary Material for the extension study protocol and statistical analysis plan.

Participants

Participants eligible to enroll in the primary study were between the ages of 3 and 15 years and had a diagnosis of CLN2 disease confirmed by deficient TPP1 enzyme activity and genetic analysis. Additional inclusion and exclusion criteria can be found in the Supplementary Material.

Written informed consent from a parent or legal guardian of each participant was obtained, and assent was obtained from the participant, if appropriate. The studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by all relevant institutional ethics boards.

The historical control group consisted of CLN2 patients who were enrolled in the DEM-CHILD NCL patient database and who were diagnosed and followed in NCL specialty centers in Hamburg, Germany and Verona, Italy.[4,8]

Procedures

Cerliponase alfa was administered via infusion (at a rate of 2·5 ml/ hour for 4 hours) through an ICV reservoir surgically implanted into the lateral cerebral ventricle. Following the dose-escalation phase of the primary study and during the extension study, participants received 300 mg cerliponase alfa every 2 weeks. Due to the potential for hypersensitivity reactions, prophylactic antihistamine and/or antipyretic could be administered at the investigator's discretion approximately 30 minutes before each infusion. During the extension study, the CLN2 Clinical Rating Scale was administered every 8 weeks. Safety assessments included brief physical exam, AEs, concomitant medication use, vital signs, and cerebrospinal fluid (CSF) surveillance every 2 weeks; clinical laboratory tests, neurologic exam, visual acuity tests, and CSF/serum collection for immunogenicity tests every 12 weeks; and MRI, quality of life assessments, developmental assessments, electrocardiograms, and electroencephalograms every 24 weeks. Complete physical examination was performed every 48 weeks. The attribution of AEs to the study drug or device was determined by the investigator and was not adjudicated. Wherever possible, AEs were recorded with a diagnosis as the AE term rather than as a series of terms relating to a diagnosis.

Validated assays were used to assess serum and CSF anti-drug total antibody (TAb) and CSF neutralizing antibody (NAb) titers.[9] NAb testing was performed on baseline CSF samples and on subsequent CSF samples found to be TAb positive. Drug-specific immunoglobulin E (IgE) testing was performed on serum samples collected in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or hypersensitivity adverse event (HAE) of Grade 3 or higher. See appendix for additional details regarding immunogenicity monitoring methods.

Outcomes

The primary efficacy outcome of study 190-202 was the time to first unreversed 2-point decline or unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale, comparing treated patients with historical untreated controls (see Supplementary Material for details regarding the scale and its assessment).[10-12] An unreversed 2-point decline was defined as a decline that had not returned to within 1 point of baseline score by the last

assessment. The same principal investigator, or a qualified physician designated by the principal investigator, who was continuously trained on the CLN2 Clinical Rating Scale, assessed subjects at their study site.

Pre-specified supportive analyses of the primary efficacy outcome included assessment of time to first unreversed 2-point decline or a score of 0 on the separate motor and language domains of the CLN2 Clinical Rating Scale; time to unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale; rate of decline in the combined motor-language score; and change from baseline in the combined motor-language score, total CLN2 Clinical Rating Scale score (motor, language, vision, seizure domains), and individual domain scores. For each, outcomes in treated patients were compared with historical untreated controls.

The secondary efficacy endpoint was brain atrophy, evaluated by volumetric MRI in treated patients considering one or more of the following: whole brain volume, percent cerebrospinal fluid, percent gray matter, percent white matter, whole brain apparent diffusion coefficient and cortical thickness. Data on whole brain percent gray matter is presented here as it is the most well described in published natural history studies of CLN2 disease patients.[13] Analyses of additional MRI parameters, pooling data from multiple studies, are ongoing and will be reported separately.

Exploratory efficacy endpoints were survival, CSF and plasma biomarkers, developmental milestones (Denver II Development Scale), anti-epileptic treatment, Quality of Life (Pediatric Quality of Life Inventory [PedsQL] Parent Report for Toddlers and Parent Family Impact; CLN2 disease-based Quality of Life), retinal anatomy using optical coherence tomography, visual acuity, and electroencephalograms. Analyses of survival, quality of life, and developmental milestone data are presented in the Supplementary Materials. Data collected on CSF and plasma biomarkers, anti-epileptic treatment, retinal anatomy, visual acuity, and electroencephalograms are not reported here. Retinal anatomy and visual acuity assessments were only conducted in the extension study and were added as part of a protocol amendment, limiting their utility for evaluating progression of retinal disease due to lack of baseline and data over the first year of treatment. Data on neurofilament light (NF-L) as a potential biomarker for CLN2 disease collected in the primary and extension studies have been published elsewhere.[14] Data on other outcomes are the subject of ongoing analyses.

Statistical Analysis

No formal sample size calculations were performed: sample size for the primary study was based on the ultra-rare nature of CLN2 disease.

All participants who received more than 1 dose of cerliponase alfa were included in efficacy analyses and were compared with evaluable untreated historical controls enrolled in the DEM-CHILD NCL registry.[4,8] Baseline measurement for treated patients was defined as the last observation preceding the first administration of a 300 mg dose of cerliponase alfa. For patients in the historical control cohort, baseline score on the combined motor-language scale was defined as the first score of less than 6 occurring at the age of 36 months or more; the age at baseline assessment was calculated as the midpoint of the age range of assessments at the time this score was obtained.

Kaplan-Meier methods and the Cox proportional-hazards model were used to compare the time to unreversed 2-point decline or a score of 0 and the time to unreversed score of 0 on the

combined motor-language domains for treated patients and historical controls. Follow-up was from baseline to time of unreversed 2-point decline or score zero (event) or time of last CLN2 clinical rating scale assessment (censoring). The Cox model included baseline combined motor-language score, age, genotype (common alleles), and sex as covariates. Similar analyses were performed to examine differences in the motor and language domain scores alone, as well as time to score of 0 on the combined motor-language domains.

Rate of decline in the combined motor-language score was calculated as the change from baseline to last assessment with a score of more than 0 divided by the length of follow-up and compared between treated patients and historical controls using a 2-sample t-test based on unequal variances. Change from baseline in the CLN2 Clinical Rating Scale score was calculated for 2 domains (motor and language; range 0-6), 4 domains (motor, language, vision, and seizures; range, 0-12), and for individual domains (for each, range 0-3) and compared between treated patients and historical controls. Confirmatory analyses of change from baseline were also performed in matched cohorts (see Supplementary Methods).

Changes in brain volume for treated patients, assessed by non-contrast whole brain MRI, were summarized by timepoint as absolute and percent changes from baseline.

Methods used for analyses of exploratory efficacy endpoints (mortality, quality of life, and developmental milestones) are described in the Supplementary Materials.

Safety data presented include all AEs reported in the primary and extension studies from the last observation preceding device implantation until 6 months after either the last administration of study drug or early termination visit. Relationships between immunogenicity and safety or efficacy endpoints were explored for TAb-negative and TAb-positive patients using box-plots. Seizure AEs mapping to the Convulsions Standardized MedDRA Query (SMQ) were assessed for consecutive 24-week intervals.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Role of the Funding Source

The study was funded by BioMarin Pharmaceutical, Inc. The funder designed the studies with input from the investigators, provided the study medication, and analyzed the data collected from the trial sites. Assistance with manuscript preparation was provided by a medical writer employed by the funder.

RESULTS

Participants were screened and enrolled in the primary study between 13 September 2013 and 22 December 2014. All 24 participants who enrolled in the primary study were evaluated for safety. One participant withdrew from the primary study at the parents' request after receiving 1 dose of the study drug due to an inability to comply with study procedures, and was excluded from efficacy analyses. Incidence rates for AEs may therefore be slightly under-reported due to the very early termination of 1 participant. Of the 23 participants who received more than 1 dose of cerliponase alfa, all completed the primary study and enrolled in the extension study. Seventeen of the 23 participants who enrolled in the extension study completed the planned follow-up. Six participants withdrew from the extension study: 4 due to relocation or switch to commercial therapy and 2 due to meeting study stopping criteria, having a score of 0 in the combined motor-language domains assessed at consecutive study visits. For participants who

withdrew, all data up until the last available assessment were included for analysis. The database of untreated historical controls contained 69 individuals of whom 42 satisfied the criteria for comparability to the treated population.

Demographic and clinical characteristics of enrolled participants are summarized in Table 1. The population included 9 males (37.5%) and 15 (62.5%) females. The mean (SD) age at the time of enrollment in the primary study was 4·9 (1·3) years and the mean (SD) score on the combined motor-language domains of the CLN2 Clinical Rating Scale at 300 mg baseline was 3·5 (1·2), (range, 1 to 6). The safety population (n=24) was followed for a mean (SD) treatment duration of 263·2 (67·9) weeks (range, 0·1 to 309·1). The 23 participants who enrolled in the extension study and were evaluated for efficacy received 300 mg of cerliponase alfa for a mean (SD) of 272·1 (37·4) weeks (range, 162·1–300·1). A total of 3142 infusions were administered across both studies, with 3113 infusions at the 300 mg dose; the mean (SD) number of infusions per participant at any dose was 130·9 (33·5).

Treated patients were significantly less likely than historical controls to have an unreversed 2-point decline or a score of 0 in the combined motor-language domains (Figure 1A; HR, 0·14; 95% CI, 0·06 to 0·33; p<0·0001). The median (95% CI) time to event was 272 weeks (lower CI, 199 weeks; upper CI not estimable) in treated patients compared to 49 weeks (95% CI, 39 to 58) in historical controls. Similar results were observed for the motor and language domains individually (Figure S2A and S2B, respectively). Treated patients were also significantly less likely than historical controls to reach an unreversed score of 0 in the combined motor-language domains, representing complete loss of ability to ambulate and communicate (Figure 1B; HR, 0·02; 95% CI, 0·00 to 0·08; p<0·0001). The median time to reach an unreversed score of 0 was 109 weeks (95% CI, 90 to 129) in historical controls; only 3 treated patients reached an unreversed score of 0 by study completion and the median time to score 0 was not estimable. All 3 patients who reached a score of 0 had a baseline motor-language score of 3: one reached a score of 0 only at the study completion visit (week 288), one patient reached a score of 0 at week 264, and one patient at week 193.

The estimated mean (SD) rate of decline in the combined motor-language score was 0·38 (0·50) points per 48 weeks among treated patients (range: 0·00 to 2·18) and 2·13 (0·95) points per 48 weeks among historical controls (range: 0·45 to 4·27), a mean difference of 1·75 points (95% CI, 1·39 to 2·11; p<0·0001). After adjustment for baseline covariates (age, baseline motor-language score, sex, and genotype), the rate of decline was 0·64 (0·09) points per 48 weeks among the treated patients and 1·99 (0·14) points per 48 weeks among historical controls, a mean difference of 1·35 points (95% CI, 0·99 to 1·71; p<0·0001).

Combined motor-language score was seen to decline rapidly in the historical controls (Figure 1C), with scores approaching 0 by week 145. Treated patients showed a gradual decline from baseline over time reaching a mean (SD) score of 2·8 (1·43) points by week 145 and 1·8 [1·07] by week 313. Similarly, a rapid decline in total CLN2 Clinical Rating Scale score (motor, language, vision, and seizure domains) was observed for historical controls compared with a more gradual decline in treated patients (Figure 1D). Similar results were attained in analyses performed in matched cohorts (see supplemental results; Figures S3-S5).

Data on change from baseline in individual CLN2 Clinical Rating Scale domain scores are shown in Figure S6 and Table S2. Vision domain score was seen to decline in both groups, albeit

more rapidly in the historical controls (Figure S6). Treated patients showed a mean decline of 1.4 points from baseline to week 289 compared with a decline of 2.3 points for historical controls (Table S2). The seizure domain score provides an assessment of the frequency of tonic-clonic seizures: mean (SD) seizure domain score increased from 1·7 (1·2) at baseline to 2·4 (0·8) at week 289 in treated patients but decreased from 1·7 (1·1) to 0·7 (1·2) in historical controls, indicating declining frequency of seizures in treated patients and increasing frequency of seizures in historical controls (Table S2 and Figure S6).

Mean percentage change from baseline in total gray matter volume of treated patients, assessed by MRI, is shown in Figure 2. The mean absolute change from baseline to week 49 (end of the primary study) was -9·7%. At week 145, the observed change from baseline was -13·4% and, as of the last observation in the study, the change from baseline was -14·7%.

Data on exploratory efficacy endpoints (mortality [Figure S7], quality of life [Tables S3 and S4], and developmental milestones [Table S5]) are presented in the Supplementary Materials.

All participants experienced at least 1 AE (Table 2 and Table S6). Most AEs were Grade 1 or 2 in severity; 18 participants (75%) had at least one AE of Grade 3 and 3 participants (13%) had a Grade 4 AE. Grade 4 AEs were blindness, pyelonephritis, and status epilepticus. Fifteen participants experienced 52 AEs leading to dose interruptions; no AEs led to dose reduction. There were no deaths and no study discontinuations because of an AE. A total of 237 AEs in 23 participants were considered related to study drug; the most common drug-related AEs were pyrexia (127 events in 11 participants), hypersensitivity (16 events in 10 participants), seizure (14 events in 9 participants), vomiting (15 events in 6 participants), and epilepsy (4 events in 4 participants).

Overall, 107 serious adverse events (SAEs) were reported in 21 participants (88%) (Table 2 and Table S7). A total of 12 SAEs in 8 participants were considered related to study drug; the most common drug-related SAEs were hypersensitivity (9 events in 7 participants), infusion-associated reaction (2 events in 1 participant), pleocytosis (1 event in 1 participant).

Eighteen participants (75%) had a total of 56 hypersensitivity AEs (HAEs; Table S8); 29 were Grade 1, 19 were Grade 2, and 8 were Grade 3. There were no AEs of anaphylaxis or anaphylactoid reactions according to the criteria of the US National Institute of Allergy and Infectious Diseases. Twenty-one participants (88%) had a combined 79 device-related AEs (Table S9): the most common were device-related infections (15 events in 9 participants) and device end-of-service events, representing prophylactic replacement of the ICV device (13 events in 13 participants). A total of 29 device-related SAEs were reported in 16 participants, including 12 device-related infections in 7 participants. A total of 14 device-related AEs in 7 participants led to ICV device replacement (2 participants had 3 device replacement; 2 participants had 2 replacements, and 3 participants had a single replacement): device-related infection (9 events in 6 participants), device leakage (2 events in 2 participants), device deployment issue (2 events in 2 participants), and device malfunction (1 event in 1 participant). Device-related infections were managed with intravenous antibiotics, with the specific agent used being determined based on the organism identified. In all cases, the ICV device was successfully replaced without complication and without discontinuation of study drug.

A total of 7 participants (29%) experienced 15 cardiovascular events (most common were: bradycardia, 4 events; hypotension, 4 events; hematoma, 2 events) and 23 participants (96%) experienced 693 events mapping to the convulsions Standardized MedDRA Query (Table S10).

No events of hydrocephalus, meningitis, or unexpected rapid decline in motor-language score were reported. The proportion of participants who reported ≥1 event of convulsions as an AE declined from 88% (n=21) during weeks 0-24, reaching a nadir of 26% (n=23) during weeks >144 to 168, before increasing to 59% (n=13) in weeks >216 (Figure S8).

The anti-drug antibody (ADA) response in all participants by time on treatment is displayed for CSF TAb (Figure S9A) and serum TAb (Figure S9B). CSF TAb response was detected in 10 participants (42%); earliest time to onset was 13 weeks. CSF TAb titers returned to undetectable levels in 9 out of 10 ADA positive participants by the end of the study. Serum TAb response was detected in 19 participants (79%); titers were sustained in 12/19 (63%), declined in 5/19 (26%), and reverted to undetectable in 2/19 (11%) by the end of the study. Low titer NAb were detected in the CSF of 3 participants (13%) at a single visit. Change from baseline in the combined motor-language score was comparable between CSF TAb-negative and TAb-positive participants (Figure S10). Six participants reported 8 Grade 3 HAEs; however, no association was found between serum ADA titer and either the incidence or severity of HAEs (Figure S11A and S11B, respectively). Serum samples collected from all participants reporting Grade 3 HAEs were tested and found negative for drug-specific IgE.

DISCUSSION

Intracerebroventricular cerliponase alfa is the first disease-modifying treatment approved for CLN2 disease. Treatment with 300 mg cerliponase alfa every other week for at least 96 weeks was shown to result in meaningful preservation of motor and language function, with acceptable safety and tolerability,[7] and cerliponase alfa has increasingly become the standard of care for children with CLN2 disease, where available.[15] In this report, we confirm that slowing of clinical disease progression is maintained through >5 years of treatment, with expected but manageable safety events. After completion of the 240-week treatment period of the study, participants were not required to continue on treatment. However, all who completed the treatment period did indeed continue to receive infusions and remained on treatment at the time of the 6-month safety follow-up visit.

After receiving cerliponase alfa for at least 162 weeks at the 300 mg dose, treated patients were found to be less likely than historical untreated controls to experience an unreversed 2-point decline or a score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale. The mean (SD) rate of decline in the combined motor-language domain score was 1·75 points/48 weeks lower for treated patients than for historical controls. Rates of decline were comparable to those reported after 96 weeks of treatment suggesting that attenuation of disease progression is maintained. Although a decline in motor-language score was still seen in treated patients, the attenuation relative to historical controls was clinically meaningful: by the end of study, motor-language score in treated patients had declined by approximately 1.5 points to a median score of 2: at this level children require assistance to walk and have limited language. In comparison, for historical controls, the median time to reach a motor-language score of 0, representing complete loss of ambulation and ability to communicate through speech, was 109 weeks.

Seizures are a predominant feature of CLN2 disease and remain a significant burden throughout disease progression. CLN2 Clinical Rating Scale seizure domain scores indicated a reduction in the frequency of tonic-clonic seizures in treated patients, whereas an increase in frequency was observed in historical controls, suggesting that treatment may also have some benefit on seizures.

Consistent with this, the proportion of participants with convulsions AEs declined over time. However, it should be noted that changes in use of antiepileptic drugs, concurrent illnesses, and brain atrophy over disease progression may also affect seizure frequency and severity.

Patients with CLN2 disease suffer from progressive loss of vision and are typically blind by the age of 7-10 years.[11] ICV administration of cerliponase alfa is not expected to have an impact on the retina, and decline in vision accompanied by progressive retinal degradation has been documented in patients receiving treatment.[16] Consistent with this, scores on the vision domain of the CLN2 Clinical Rating Scale were seen to decline in both treated and historical control patients, although the decline was somewhat delayed in treated patients, suggesting that despite the lack of effect on retinal degradation, there may be an impact of treatment on the occipital visual cortex. Studies in canine models of CLN2 disease have demonstrated that intravitreal injection of cerliponase alfa can preserve retinal structure and function[17,18] and clinical trials evaluating the impact of intravitreal cerliponase alfa are ongoing (NCT05152914).

Among treated patients, total gray matter volume declined over the duration of the study. However, most of this decline occurred over the first 49 weeks of treatment, with a smaller incremental loss by week 97, after which little further change was observed. This may suggest that there is an initial loss of cortical gray matter followed by stabilization. Interpretation of these findings is limited by the lack of comparator data for historical untreated controls. However, Loebel et al. have shown progressive loss of supratentorial cortical gray matter (up to 12·5 % per year) in a longitudinal cohort of untreated CLN2 disease patients.[13]

Time to death was evaluated as an exploratory outcome in the study. Median age of death for historical untreated controls was 10·4 years; none of the treated patients died during the study. In CLN2 disease, symptomatic care (e.g., mechanical ventilation, gastrostomy tube feeding) may prolong life, but such measures do not generally alter disease progression and thus prolongation of life may be predominantly in the most progressed stages of disease. Supportive analyses of the primary efficacy endpoint demonstrating a delay in time to reach a score of zero suggest that the increased survival observed in patients treated with cerliponase alfa is accompanied by preservation of function. Assessments of quality of life and achievement of developmental milestones were also considered as exploratory efficacy endpoints in the study. Quality of life scores showed a substantial impairment at study baseline, reflecting the burden of disease and extent of progression in these patients at the time of enrollment. Scores in PedsQL domains relating to physical, social and school functioning were lower at end of study compared to baseline, while the others were minimally changed or higher. Interpretation of the significance of these changes is limited by the lack of comparator data from historical controls as well as the lack of defined, population-specific clinically important difference estimates. Moreover, the high degree of variability seen suggests the need to evaluate these outcomes at the patient level and in the context of disease progression and intercurrent events.

The safety profile of ICV cerliponase alfa was similar to that observed after 96 weeks. The most common SAEs reflect treatment with an exogenous protein and complications arising from use of the ICV device. All participants who experienced Grade 3 hypersensitivity reactions tested negative for the presence of drug-specific IgE antibodies, a hallmark of acute type I hypersensitivity reactions.[19-21] The impact of immunogenicity on safety and efficacy was consistent with previously reported findings based on up to 129 weeks of treatment.[9]

All participants who experienced ICV device-related infections, or who required replacement of the device for other reasons, continued therapy after removal of the device, intravenous antibiotic treatment when appropriate, and subsequent device replacement. The occurrence of device-related infections emphasizes the importance of strict adherence to sterile technique at all times when preparing and administering cerliponase alfa.[22,23] In addition to ICV device replacement following infections or complications, replacement is recommended prior to 4 years of use due to the potential for material degradation.[24] Participants in this study had received treatment for approximately 5 years by its conclusion and more than half were observed to have had a prophylactic device replacement.

The major limitation of both the primary and extension studies is its open-label, non-randomized design and lack of a contemporaneous control group. The natural history cohort had less frequent assessments and a substantially longer epoch of assessment than the treatment group. Bias could arise if changing standard of care had an impact on motor-language assessment in the control group. We note, however, that the natural history database is the largest available and that the duration of follow-up for both natural history patients and treated patients was substantial. To limit the likelihood that findings were the result of bias, a number of supportive analyses were conducted, including patient-level matching and covariate adjustments. All such analyses confirmed the observed treatment benefit, however the potential for unmeasured confounding cannot be excluded. Additionally, for analyses of survival and time to loss of function (motor-language score 0) where few events were observed in treated patients, length of follow-up time is a limitation and although penalization methods were used for analyses, sparse-data bias may remain.[25] The motor-language score itself has inherent limitations in that it does not capture many important aspects of CLN2 disease and, moreover, lacks granularity with domain scores covering a comparatively wide range of abilities. However, it was selected as the primary efficacy outcome in this study because it provided an objective assessment that could be used to compare outcomes in treated patients with those of historical controls.

In conclusion, data from this study demonstrate that long-term ICV administration of cerliponase alfa in children with CLN2 disease slows decline in critical motor and language function compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these were manageable and did not result in treatment discontinuation. A further study in an expanded cohort including children younger than 3 years of age (NCT02678689) will explore outcomes following initiation of cerliponase alfa treatment in presymptomatic children.[26]

Contributions

All authors made substantial contributions to the acquisition and interpretation of study data; revised the manuscript critically for important intellectual content; approved the final version to be published; and are accountable for all aspects of the work. PS conducted the data analyses with consultation from JCP. All the authors vouch for the accuracy and completeness of the study results, adherence to the protocol, and reporting of AEs. The corresponding author (AS) and sponsor authors directly accessed the study data. All authors had full access, if requested, to all the data in the study and accept responsibility to submit for publication. The manuscript was drafted by a medical writer (Abigail Hunt, an employee of BioMarin) under the direction of the authors.

Declaration of interests

AS and MN have received payments to their institution as a study site according to clinical trial budget, medical writing support, honoraria and travel support from BioMarin Pharmaceutical Inc; EDLR has received salary support as the primary investigator and salary support for the research personnel, honoraria and travel support from BioMarin Pharmaceutical Inc and consulting fees from Zogenix; NS has received consulting fees from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB, Takeda, and Angeun; honoraria from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB and Zogenix; and travel fees BioMarin Pharmaceutical Inc and Jazz Pharma; PG has received payments to his institution as a study site according to clinical trial budget, honoraria and travel support from BioMarin Pharmaceutical Inc; MT has received honoraria from BioMarin Pharmaceutical Inc; SCA has received research salary support from BioMarin Pharmaceutical Inc, research effort support for study on erenumab from Amgen, research effort support for study on Rimegepant from Pfizer, grant support for fellowship training from NINDS/Neuronext and honoraria as associate editor from Pediatric Neurology; DJB and JPD have received contractor fees paid by BioMarin Pharmaceutical Inc for analyzing imaging data that appears in the paper; PS is an employee and stockholder of BioMarin Pharmaceutical Inc; SB and ACherukuri are employees of BioMarin Pharmaceutical Inc; JLCP is an employee & stockholder of BioMarin Pharmaceutical Inc and a scientific advisor for NPKUA; AChakrapani, CS, EW, and LMW reported no conflicts of interest.

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Data sharing

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes.

Additional supporting documents may be available upon request.

Investigators will be able to request access to these data and supporting documents via a data sharing portal beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of relevant product.

Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology.

Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com/patients/publication-data-request/ to determine whether access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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Figure Legends

Figure 1: CLN2 Clinical Rating Scale Outcomes
Panels A and B show Kaplan-Meier curves for time to unreversed 2-point decline from baseline or a score of 0 (Panel A), and time to unreversed score of 0 (Panel B) in the combined score for motor and language domains. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Panels C and D show change from baseline in the score for motor and language function (Panel C) and in the score for all four domains of the CLN2 Rating Scale (motor, language, vision, and seizure domains; Panel D) for treated patients and historical controls. Error bars indicate 95% confidence intervals.

Figure 2: Change from Baseline in Total Gray Matter Volume among Treated Patients
Graph shows the percent change from baseline in total gray matter volume among treated patients. Error bars represent 95% confidence intervals. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Numbers shown on the figure represent the number of patients with available data at each time point.

References

1. Chang M, Cooper JD, Davidson BL, et al. CLN2. In: Mole SE, Williams Re, Goebel HH, eds. The Neuronal Ceroid Lipofuscinoses (Batten Disease). 2nd ed; 2011: 80-109.
2. Sleat DE, Gin RM, Sohar I, et al. Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. *Am J Hum Genet* 1999; **64**(6): 1511-23.
3. Fietz M, AlSayed M, Burke D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. *Mol Genet Metab* 2016; **119**(1-2): 160-7.
4. Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. *Lancet Child Adolesc Health* 2018; **2**(8): 582-90.
5. Kohlschutter A, Schulz A. CLN2 Disease (Classic Late Infantile Neuronal Ceroid Lipofuscinosis). *Pediatr Endocrinol Rev* 2016; **13 Suppl 1**: 682-8.
6. Schulz A, Kohlschutter A, Mink J, Simonati A, Williams R. NCL diseases - clinical perspectives. *Biochim Biophys Acta* 2013; **1832**(11): 1801-6.
7. Schulz A, Ajayi T, Specchio N, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. *N Engl J Med* 2018; **378**(20): 1898-907.
8. Schulz A, Simonati A, Laine M, Williams R, Kohlschutter A, Nickel M. The DEM-CHILD NCL Patient Database: A tool for the evaluation of therapies in neuronal ceroid lipofuscinoses (NCL). *European Journal of Pediatric Neurology* 2015; **19**: S16.
9. Cherukuri A, Cahan H, de Hart G, et al. Immunogenicity to cerliponase alfa intracerebroventricular enzyme replacement therapy for CLN2 disease: Results from a Phase 1/2 study. *Clin Immunol* 2018; **197**: 68-76.
10. Wyrwich KW, Schulz A, Nickel M, et al. An adapted clinical measurement tool for the key symptoms of CLN2 disease. *Journal of Inborn Errors of Metabolism and Screening* 2018; **6**: 1-7.
11. Steinfeld R, Heim P, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. *Am J Med Genet* 2002; **112**(4): 347-54.
12. Worgall S, Kekatpure MV, Heier L, et al. Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. *Neurology* 2007; **69**(6): 521-35.
13. Lobel U, Sedlacik J, Nickel M, et al. Volumetric Description of Brain Atrophy in Neuronal Ceroid Lipofuscinosis 2: Supratentorial Gray Matter Shows Uniform Disease Progression. *AJNR Am J Neuroradiol* 2016; **37**(10): 1938-43.
14. Ru Y, Corado C, Soon RK, Jr., et al. Neurofilament light is a treatment-responsive biomarker in CLN2 disease. *Ann Clin Transl Neurol* 2019; **6**(12): 2437-47.
15. Mole SE, Schulz A, Badoe E, et al. Guidelines on the diagnosis, clinical assessments, treatment and management for CLN2 disease patients. *Orphanet J Rare Dis* 2021; **16**(1): 185.
16. Dulz S, Schwering C, Wildner J, et al. Ongoing retinal degeneration despite intraventricular enzyme replacement therapy with cerliponase alfa in late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2 disease). *Br J Ophthalmol* 2022.
17. Whiting REH, Pearce JW, Vansteenkiste DP, et al. Intravitreal enzyme replacement preserves retinal structure and function in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **197**: 108130.

18. Whiting REH, Robinson Kick G, Ota-Kuroki J, et al. Intravitreal enzyme replacement inhibits progression of retinal degeneration in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **198**: 108135.
19. de Las Vecillas Sanchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug Hypersensitivity and Desensitizations: Mechanisms and New Approaches. *Int J Mol Sci* 2017; **18**(6).
20. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. *Am Fam Physician* 2003; **68**(9): 1781-90.
21. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011; **127**(3 Suppl): S67-73.
22. de Los Reyes E, Lehwald L, Augustine EF, et al. Intracerebroventricular Cerliponase Alfa for Neuronal Ceroid Lipofuscinosis Type 2 Disease: Clinical Practice Considerations From US Clinics. *Pediatr Neurol* 2020; **110**: 64-70.
23. Schwering C, Kammler G, Wibbeler E, et al. Development of the "Hamburg Best Practice Guidelines for ICV-Enzyme Replacement therapy (ERT) in CLN2 Disease" Based on 6 Years Treatment Experience in 48 Patients. *J Child Neurol* 2021; **36**(8): 635-41.
24. Inc. BP. Prescribing Information: BRINEURA (cerliponase alfa) injection, for intraventricular use. 2020.
25. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016; **352**: i1981.
26. Schulz A, de Los Reyes E, Specchio N, et al. Cerliponase alfa for the treatment of CLN2 disease in an expanded patient cohort including children younger than three years: Interim results from an ongoing clinical study. *Mol Genet Metab* 2021; **132**(2): S95.

620 **Table 1. Demographic and Clinical Characteristics of Participants at Baseline (Safety Population)***

	Participants (n=24)
Age at enrollment, years	
Mean (SD)	4·9 (1·28)
Median (IQR)	4·6 (4.0, 5.5)
Range	3·1, 8·9
Sex, n (%)	
Male	9 (38)
Female	15 (63)
Race, n (%)	
Asian	1 (4)
Black	0
White	23 (96)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	1 (4)
Not Hispanic or Latino	23 (96)
Baseline motor/language CLN2 Rating Scale score†	
Mean (SD)	3·5 (1·2)
Median (IQR)	3·0 (3.0, 4.0)
Score, n (%)	
6	2 (8)
5	2 (8)
4	6 (25)
3	11 (46)
2	2 (8)
1	1 (4)
Genotype, n (%)	
2 common alleles‡	9 (38)
1 common and 1 uncommon allele§	8 (33)
2 uncommon alleles	7 (29)

* Percentages may not sum to 100 as a result of rounding
† Score was assessed just prior to first 300 mg dose; higher scores represent higher functioning
‡ Common alleles are c.622C>T and c.509-1G>C
§ Uncommon alleles were c.1448G>A, c.380G>A, c.833A>G, c.1015C>T, c.731T>C, c230-13T>A c.1261T>A, and c.1087delinsTT

SD, standard deviation; IQR, interquartile range

621

622 **Table 2: Adverse Events: Safety Population**

	Participants (n=24)623
Common adverse events, n (%)	
Upper respiratory tract infection	21 (88)
Pyrexia	20 (83)
Viral upper respiratory tract infection	19 (79)
Vomiting	19 (79)
Generalized tonic-clonic seizure	16 (67)
Seizure	14 (58)
Constipation	13 (54)
Device end of service	13 (54)
Dysphagia	13 (54)
Epilepsy	13 (54)
Rhinitis	13 (54)
Gait disturbance	12 (50)
Cough	11 (46)
Dystonia	11 (46)
Tremor	11 (46)
Visual impairmemt	11 (46)
Hypersensitivity	10 (42)
Myoclonus	10 (42)
Device-related infection	9 (38)
Diarrhoea	9 (38)
Extensor plantar response	9 (38)
Gastroenteritis	9 (38)
Needle issue	9 (38)
Sleep disorder	9 (38)
Viral infection	9 (38)
Serious adverse events, n (%)	
Any serious adverse event	21 (88)
Device end of service	13 (54)
Hypersensitivity	7 (29)
Device-related infection	7 (29)
Upper respiratory tract infection	5 (21)
Dysphagia	4 (17)
Gastroenteritis	4 (17)
Pleocytosis	3 (13)
Dental caries	2 (8)
Device deployment issue*	2 (8)
Epilepsy	2 (8)
Pharyngitis bacterial	2 (8)
Pyelonephritis	2 (8)
Pyrexia	2 (8)

Common adverse events shown are those reported in more than 35% of the participants.
Serious adverse events shown are those reported in more than 1 participant.
*Device deployment issues included procedural issues during the placement or positioning of the intracerebroventricular device.

Figure 1

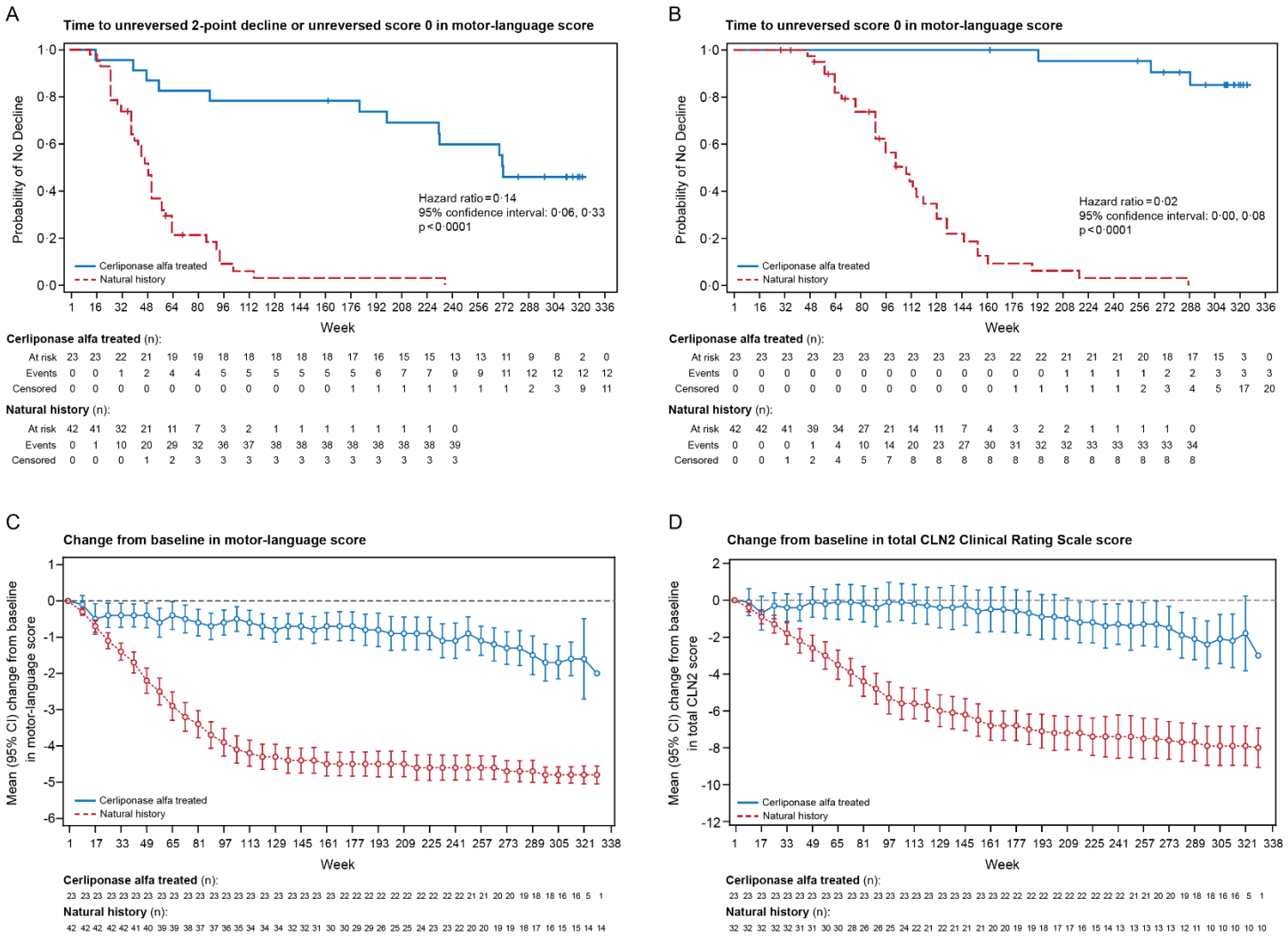
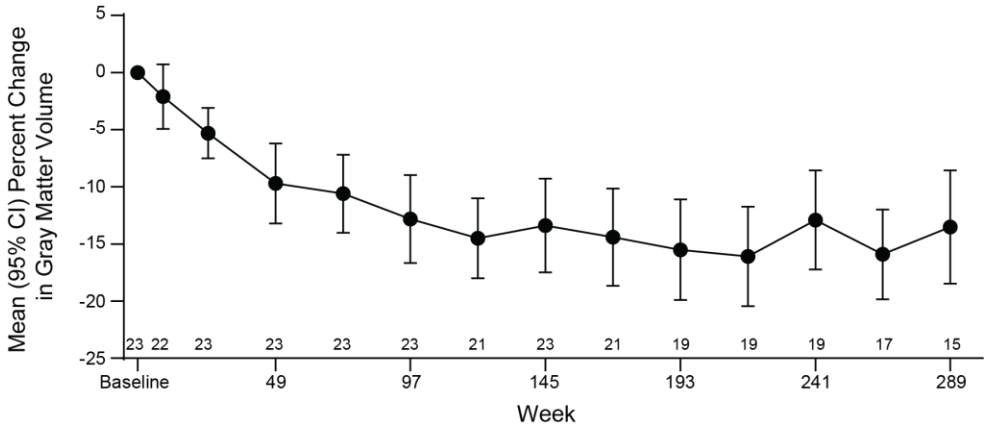

A
Time to unreversed 2-point decline or unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·14
95% confidence interval: 0·06, 0·33
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 22 21 19 19 18 18 18 18 18 17 16 15 15 13 13 11 9 8 2 0
Events 0 0 1 2 4 4 5 5 5 5 5 5 6 7 7 9 9 11 12 12 12 12
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 2 3 9 11
Natural history (n):
At risk 42 41 32 21 11 7 3 2 1 1 1 1 1 1 1 0
Events 0 1 10 20 29 32 36 37 38 38 38 38 38 38 38 39
Censored 0 0 0 1 2 3 3 3 3 3 3 3 3 3 3 3
B
Time to unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·02
95% confidence interval: 0·00, 0·08
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 23 23 23 23 23 23 23 23 23 22 22 21 21 21 20 18 17 15 3 0
Events 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 2 2 3 3 3
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 2 3 4 5 17 20
Natural history (n):
At risk 42 42 41 39 34 27 21 14 11 7 4 3 2 2 1 1 1 1 0
Events 0 0 0 1 4 10 14 20 23 27 30 31 32 32 33 33 33 33 34
Censored 0 0 1 2 4 5 7 8 8 8 8 8 8 8 8 8 8 8 8
C
Change from baseline in motor-language score
Mean (95% CI) change from baseline in motor-language score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 18 18 16 16 5 1
Natural history (n):
42 42 42 42 42 41 40 39 39 38 37 37 36 35 34 34 34 32 32 31 30 30 29 29 26 25 25 24 23 23 22 20 20 19 19 18 17 16 15 15 14 14
D
Change from baseline in total CLN2 Clinical Rating Scale score
Mean (95% CI) change from baseline in total CLN2 score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 19 18 18 16 16 5 1
Natural history (n):
32 32 32 32 32 31 31 30 30 30 28 26 26 25 24 22 21 22 21 21 21 20 20 19 19 18 17 17 16 15 14 13 13 13 13 13 12 11 10 10 10 10 10

Figure 2



Gray Matter Volume	Baseline	49 weeks	97 weeks	145 weeks	193 weeks	241 weeks	289 weeks
Mean (SD) volume, cm^3	452·0 (87·7)	408·3 (88·5)	394·6 (89·3)	390·3 (84·3)	374·2 (89·9)	390·4 (78·4)	371·9 (54·6)
Mean % change from Baseline	-	-10%	-13%	-13%	-16%	-13%	-14%
Annualized % change from Baseline	-	-11%	-14%	-15%	-17%	-14%	-15%
Annualized interval % change	-	-11%	-4%	-1%	-3%	+2%	+1%

Long-Term Open-Label Extension Study of Cerliponase Alfa in Children with CLN2 Disease: Safety and Efficacy After >5 Years of Therapy

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ABSTRACT

BACKGROUND: Cerliponase alfa is a recombinant human tripeptidyl peptidase 1 (TPP1) enzyme replacement therapy for the treatment of neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) caused by mutations in the *TPP1* gene. The aim of this study was to determine the long-term safety and efficacy of intracerebroventricular (ICV) cerliponase alfa in children with CLN2 disease.

METHODS: This analysis includes cumulative data from a 48-week primary study (NCT01907087) and a completed 240-week open-label extension with 6-month safety follow-up (NCT02485899), conducted at 5 hospitals in Germany, Italy, the UK, and the USA between 13 September 2013 and 10 December 2020. Children aged 3-16 years with CLN2 disease confirmed by genetic analysis and enzyme testing were eligible for inclusion. Historical untreated controls with CLN2 disease in the DEM-CHILD database were used as a comparator group. Treatment was ICV infusion of 300 mg cerliponase alfa every 2 weeks. The primary efficacy outcome was time to an unreversed 2-point decline or score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale.

FINDINGS: Twenty-four participants were enrolled in the primary study (15 female, 9 male); 23 participants enrolled in the extension and received 300 mg cerliponase alfa for a mean (range) of 272·1 (162·1–300·1) weeks: 17 participants completed the extension and 7 discontinued prematurely. Treated patients were significantly less likely than historical untreated controls to have an unreversed 2-point decline or score of 0 in the combined motor-language domains (hazard ratio, 0·14; 95% confidence interval, 0·06 to 0·33; $p<0·0001$). All participants experienced ≥1 adverse event (AE) and 21 (88%) experienced a serious AE; 9 participants experienced ICV device-related infections with 9 events in 6 participants resulting in device replacement. There were no study discontinuations because of an AE. There were no deaths and treated patients were significantly less likely to die than historical controls.

INTERPRETATION: Cerliponase alfa treatment over a period of >5 years was seen to confer a clinically meaningful slowing of motor and language function decline in children with CLN2 disease. Although our study is limited by the lack of a contemporaneous control group, the results provide critical insights into the outcomes of long-term treatment.

FUNDING: BioMarin Pharmaceutical Inc.

RESEARCH IN CONTEXT

Evidence before this study

We conducted a PubMed search for clinical trials published between 1 January 1966 and 24 May 2023, using the text word search terms “CLN2 disease,” “neuronal ceroid lipofuscinosis type 2,” or “Batten disease”, and “cerliponase alfa” without language restriction. To date, the safety, efficacy, and immunogenicity of cerliponase alfa have been assessed in a completed multicentre, single-arm, dose-escalation clinical study (NCT01907087, EudraCT 2012-005430-11) after all participants had received at least 48 weeks of 300 mg dosing and an interim analysis (an additional 48 weeks of data) of a 240-week extension study (NCT02485899, EudraCT 2014-003480-37). Compared with historical controls, patients treated with the recommended 300 mg cerliponase alfa every 2 weeks for at least 96 weeks experienced a statistically significant slowing of decline in motor and language function. Adverse events, including seizures, pyrexia, vomiting, device-related infections, and hypersensitivity reactions, were shown to be manageable and did not result in treatment discontinuation. These data represent a clinically meaningful preservation of motor and language function and an acceptable risk profile and have increasingly led to cerliponase alfa becoming the standard of care for children with CLN2 disease, where this treatment is available.

Added value of this study

This report presents final long-term outcomes (>5 years of treatment) based on cumulative data from the primary and extension studies of safety and efficacy of cerliponase alfa in children with CLN2 disease. Participants in the study ranged in age between 3.1 and 8.9 years at the time of enrolment. After >5 years of follow-up in the long-term extension study, all patients had reached the age at which disease progression would be expected to be very advanced, and thus the data presented here provide additional information about the efficacy of treatment through the expected phase of most rapid decline. Moreover, many patients had reached an age exceeding the typical life expectancy for untreated patients, and a significant impact of treatment on mortality was observed.

Implications of all the available evidence

Taken together, the data show that long-term intracerebroventricular administration of 300 mg cerliponase alfa every 2 weeks in children with CLN2 disease slows decline in critical motor and language functions compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these did not result in treatment discontinuation, and immunogenicity does not appear to be a limiting factor with respect to either safety or efficacy.

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) type 2 (CLN2 disease) is a rare, rapidly progressive paediatric neurodegenerative disease caused by mutations in the tripeptidyl peptidase 1 *TPP1* gene resulting in TPP1 enzyme deficiency.[1,2] Deficient activity of TPP1 is associated with intracellular accumulation of lysosomal storage materials and neuronal cell death.[1] Children with CLN2 disease appear healthy at birth and often show delayed language acquisition before other symptoms manifest, typically at age 2-4 years with seizures and ataxia.[1,3,4] The classic late-infantile disease phenotype is characterized by loss of motor and language functions beginning at around 3 years of age and includes language regression and eventual complete loss of expressive language; new onset or worsening ataxia and complex movement disorders resulting in complete loss of independent mobility; worsening epilepsy, which may become intractable; progressive loss of ability to swallow; progressive dementia; deterioration of vision leading to blindness; and death by adolescence.[1,5,6]

In 2017, the European Medicines Agency and the United States Food and Drug Administration approved cerliponase alfa (Brineura; BioMarin Pharmaceutical Inc., Novato, CA) enzyme replacement therapy for treatment of CLN2 disease. Efficacy of cerliponase alfa was demonstrated by comparing changes in the combined motor and language domains of the CLN2 Clinical Rating Scale in treated patients with those in untreated historical controls enrolled in the DEM-CHILD NCL database.[7] Motor and language function are hallmarks of CLN2 disease severity and can be reliably measured by clinical raters: each domain of the CLN2 Clinical Rating Scale is scored from 0 to 3, with a score of 3 representing normal function and a score of 0 representing complete loss of function (Table S1). Compared with untreated historical controls, patients treated with 300 mg of cerliponase alfa for at least 96 weeks were shown to be less likely to experience an unreversed 2-point decline or score of 0 in the combined motor and language domains (hazard ratio [HR], 0·08; 95% confidence interval [CI], 0·02 to 0·23; $p<0·0001$) and had a lower mean rate of decline in motor and language function.[7] Common adverse events (AEs) in treated patients included seizures, pyrexia, vomiting, and hypersensitivity reactions.

We present cumulative data from the primary and completed open-label extension studies to assess the safety and efficacy of cerliponase alfa in children with CLN2 disease over >5 years of treatment.

METHODS

Study Design

Study 190-201 was a 48-week, single-arm, open-label, multicentre, dose-escalation study of intracerebroventricular (ICV) cerliponase alfa, conducted between September 2013 and November 2015 at 5 tertiary care hospitals (1 each in Germany, Italy, and the United States; and 2 in the United Kingdom).[7] Upon completion of the 48-week primary study, participants with a combined motor-language score of >0 on the CLN2 Clinical Rating Scale (Table S1) were eligible to enroll in study 190-202, an open-label extension study conducted between 02 February 2015 and 10 December 2020. Participants continued to receive 300 mg of ICV cerliponase alfa every 2 weeks for 240 weeks (Figure S1). A safety follow-up visit was performed 6 months after completion of the 240-week dosing period. Cumulative data from both the primary and extension studies are presented.

The primary and extension studies were registered at clinicaltrials.gov (NCT01907087 and NCT02485899) and EudraCT (2012-005430-11 and 2014-003480-37). See the Supplementary Material for the extension study protocol and statistical analysis plan.

Participants

Participants eligible to enroll in the primary study were between the ages of 3 and 15 years and had a diagnosis of CLN2 disease confirmed by deficient TPP1 enzyme activity and genetic analysis. Additional inclusion and exclusion criteria can be found in the Supplementary Material.

Written informed consent from a parent or legal guardian of each participant was obtained, and assent was obtained from the participant, if appropriate. The studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by all relevant institutional ethics boards.

The historical control group consisted of CLN2 patients who were enrolled in the DEM-CHILD NCL patient database and who were diagnosed and followed in NCL specialty centers in Hamburg, Germany and Verona, Italy.[4,8]

Procedures

Cerliponase alfa was administered via infusion (at a rate of 2·5 ml/ hour for 4 hours) through an ICV reservoir surgically implanted into the lateral cerebral ventricle. Following the dose-escalation phase of the primary study and during the extension study, participants received 300 mg cerliponase alfa every 2 weeks. Due to the potential for hypersensitivity reactions, prophylactic antihistamine and/or antipyretic could be administered at the investigator's discretion approximately 30 minutes before each infusion. During the extension study, the CLN2 Clinical Rating Scale was administered every 8 weeks. Safety assessments included brief physical exam, AEs, concomitant medication use, vital signs, and cerebrospinal fluid (CSF) surveillance every 2 weeks; clinical laboratory tests, neurologic exam, visual acuity tests, and CSF/serum collection for immunogenicity tests every 12 weeks; and MRI, quality of life assessments, developmental assessments, electrocardiograms, and electroencephalograms every 24 weeks. Complete physical examination was performed every 48 weeks. The attribution of AEs to the study drug or device was determined by the investigator and was not adjudicated. Wherever possible, AEs were recorded with a diagnosis as the AE term rather than as a series of terms relating to a diagnosis.

Validated assays were used to assess serum and CSF anti-drug total antibody (TAb) and CSF neutralizing antibody (NAb) titers.[9] NAb testing was performed on baseline CSF samples and on subsequent CSF samples found to be TAb positive. Drug-specific immunoglobulin E (IgE) testing was performed on serum samples collected in the event of a suspected anaphylactic reaction, serious hypersensitivity event, or hypersensitivity adverse event (HAE) of Grade 3 or higher. See appendix for additional details regarding immunogenicity monitoring methods.

Outcomes

The primary efficacy outcome of study 190-202 was the time to first unreversed 2-point decline or unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale, comparing treated patients with historical untreated controls (see Supplementary Material for details regarding the scale and its assessment).[10-12] An unreversed 2-point decline was defined as a decline that had not returned to within 1 point of baseline score by the last

assessment. The same principal investigator, or a qualified physician designated by the principal investigator, who was continuously trained on the CLN2 Clinical Rating Scale, assessed subjects at their study site.

Pre-specified ~~S~~supportive analyses of the primary efficacy outcome included assessment of time to first unreversed 2-point decline or a score of 0 on the separate motor and language domains of the CLN2 Clinical Rating Scale; time to unreversed score of 0 on the combined motor and language domains of the CLN2 Clinical Rating Scale; rate of decline in the combined motor-language score; and change from baseline in the combined motor-language score, total CLN2 Clinical Rating Scale score (motor, language, vision, seizure domains), and individual domain scores. For each, outcomes in treated patients were compared with historical untreated controls.

The secondary efficacy endpoint was brain atrophy, evaluated by volumetric MRI in treated patients considering one or more of the following: whole brain volume, percent cerebrospinal fluid, percent gray matter, percent white matter, whole brain apparent diffusion coefficient and cortical thickness. Data on whole brain percent gray matter is presented here as it is the most well described in published natural history studies of CLN2 disease patients.[13] Analyses of additional MRI parameters, pooling data from multiple studies, are ongoing and will be reported separately.

Exploratory efficacy endpoints were survival, CSF and plasma biomarkers, developmental milestones (Denver II Development Scale), anti-epileptic treatment, Quality of Life (Pediatric Quality of Life Inventory [PedsQL] Parent Report for Toddlers and Parent Family Impact; CLN2 disease-based Quality of Life), retinal anatomy using optical coherence tomography, visual acuity, and electroencephalograms. Analyses of survival, quality of life, and developmental milestone data are presented in the Supplementary Materials. Data collected on CSF and plasma biomarkers, anti-epileptic treatment, retinal anatomy, visual acuity, and electroencephalograms are not reported here. Retinal anatomy and visual acuity assessments were only conducted in the extension study and were added as part of a protocol amendment, limiting their utility for evaluating progression of retinal disease due to lack of baseline and data over the first year of treatment. Data on neurofilament light (NF-L) as a potential biomarker for CLN2 disease collected in the primary and extension studies have been published elsewhere.[14] Data on other outcomes are the subject of ongoing analyses.

Statistical Analysis

No formal sample size calculations were performed: sample size for the primary study was based on the ultra-rare nature of CLN2 disease.

All participants who received more than 1 dose of cerliponase alfa were included in efficacy analyses and were compared with evaluable untreated historical controls enrolled in the DEM-CHILD NCL registry.[4,8] Baseline measurement for treated patients was defined as the last observation preceding the first administration of a 300 mg dose of cerliponase alfa. For patients in the historical control cohort, baseline score on the combined motor-language scale was defined as the first score of less than 6 occurring at the age of 36 months or more; the age at baseline assessment was calculated as the midpoint of the age range of assessments at the time this score was obtained.

Kaplan-Meier methods and the Cox proportional-hazards model were used to compare the time to unreversed 2-point decline or a score of 0 and the time to unreversed score of 0 on the

combined motor-language domains for treated patients and historical controls. Follow-up was from baseline to time of unreversed 2-point decline or score zero (event) or time of last CLN2 clinical rating scale assessment (censoring). The Cox model included baseline combined motor-language score, age, genotype (common alleles), and sex as covariates. Similar analyses were performed to examine differences in the motor and language domain scores alone, as well as time to score of 0 on the combined motor-language domains.

Rate of decline in the combined motor-language score was calculated as the change from baseline to last assessment with a score of more than 0 divided by the length of follow-up and compared between treated patients and historical controls using a 2-sample t-test based on unequal variances. Change from baseline in the CLN2 Clinical Rating Scale score was calculated for 2 domains (motor and language; range 0-6), 4 domains (motor, language, vision, and seizures; range, 0-12), and for individual domains (for each, range 0-3) and compared between treated patients and historical controls. Confirmatory analyses of change from baseline were also performed in matched cohorts (see Supplementary Methods).

Changes in brain volume for treated patients, assessed by non-contrast whole brain MRI, were summarized by timepoint as absolute and percent changes from baseline.

Methods used for analyses of exploratory efficacy endpoints (mortality, quality of life, and developmental milestones) are described in the Supplementary Materials.

Safety data presented include all AEs reported in the primary and extension studies from the last observation preceding device implantation until 6 months after either the last administration of study drug or early termination visit. Relationships between immunogenicity and safety or efficacy endpoints were explored for TAb-negative and TAb-positive patients using box-plots. Seizure AEs mapping to the Convulsions Standardized MedDRA Query (SMQ) were assessed for consecutive 24-week intervals.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Role of the Funding Source

The study was funded by BioMarin Pharmaceutical, Inc. The funder designed the studies with input from the investigators, provided the study medication, and analyzed the data collected from the trial sites. ~~The corresponding author (AS) and sponsor authors directly accessed the study data. All authors had full access, if requested, to all the data in the study and accept responsibility to submit for publication.~~ Assistance with manuscript preparation was provided by a medical writer employed by the funder. ~~All the authors vouch for the accuracy and completeness of the study results, adherence to the protocol, and reporting of AEs.~~

RESULTS

Participants were screened and enrolled in the primary study between 13 September 2013 and 22 December 2014. All 24 participants who enrolled in the primary study were evaluated for safety. One participant withdrew from the primary study at the parents' request after receiving 1 dose of the study drug due to an inability to comply with study procedures, and was excluded from efficacy analyses. Incidence rates for AEs may therefore be slightly under-reported due to the very early termination of 1 participant. Of the 23 participants who received more than 1 dose of cerliponase alfa, all completed the primary study and enrolled in the extension study. Seventeen of the 23 participants who enrolled in the extension study completed the planned

follow-up. Six participants withdrew from the extension study: 4 due to relocation or switch to commercial therapy and 2 due to meeting study stopping criteria, having a score of 0 in the combined motor-language domains assessed at consecutive study visits. For participants who withdrew, all data up until the last available assessment were included for analysis. The database of untreated historical controls contained 69 individuals of whom 42 satisfied the criteria for comparability to the treated population.

Demographic and clinical characteristics of enrolled participants are summarized in Table 1. The population included 9 males (37.5%) and 15 (62.5%) females. The mean (SD) age at the time of enrollment in the primary study was 4·9 (1·3) years and the mean (SD) score on the combined motor-language domains of the CLN2 Clinical Rating Scale at 300 mg baseline was 3·5 (1·2), (range, 1 to 6). The safety population (n=24) was followed for a mean (SD) treatment duration of 263·2 (67·9) weeks (range, 0·1 to 309·1). The 23 participants who enrolled in the extension study and were evaluated for efficacy received 300 mg of cerliponase alfa for a mean (SD) of 272·1 (37·4) weeks (range, 162·1–300·1). A total of 3142 infusions were administered across both studies, with 3113 infusions at the 300 mg dose; the mean (SD) number of infusions per participant at any dose was 130·9 (33·5).

Treated patients were significantly less likely than historical controls to have an unreversed 2-point decline or a score of 0 in the combined motor-language domains (Figure 1A; HR, 0·14; 95% CI, 0·06 to 0·33; p<0·0001). The median (95% CI) time to event was 272 weeks (lower CI, 199 weeks; upper CI not estimable) in treated patients compared to 49 weeks (95% CI, 39 to 58) in historical controls. Similar results were observed for the motor and language domains individually (Figure S2A and S2B, respectively). Treated patients were also significantly less likely than historical controls to reach an unreversed score of 0 in the combined motor-language domains, representing complete loss of ability to ambulate and communicate (Figure 1B; HR, 0·02; 95% CI, 0·00 to 0·08; p<0·0001). The median time to reach an unreversed score of 0 was 109 weeks (95% CI, 90 to 129) in historical controls; only 3 treated patients reached an unreversed score of 0 by study completion and the median time to score 0 was not estimable. All 3 patients who reached a score of 0 had a baseline motor-language score of 3: one reached a score of 0 only at the study completion visit (week 288), one patient reached a score of 0 at week 264, and one patient at week 193.

The estimated mean (SD) rate of decline in the combined motor-language score was 0·38 (0·50) points per 48 weeks among treated patients (range: 0·00 to 2·18) and 2·13 (0·95) points per 48 weeks among historical controls (range: 0·45 to 4·27), a mean difference of 1·75 points (95% CI, 1·39 to 2·11; p<0·0001). After adjustment for baseline covariates (age, baseline motor-language score, sex, and genotype), the rate of decline was 0·64 (0·09) points per 48 weeks among the treated patients and 1·99 (0·14) points per 48 weeks among historical controls, a mean difference of 1·35 points (95% CI, 0·99 to 1·71; p<0·0001).

Combined motor-language score was seen to decline rapidly in the historical controls (Figure 1C), with scores approaching 0 by week 145. Treated patients showed a gradual decline from baseline over time reaching a mean (SD) score of 2·8 (1·43) points by week 145 and 1·8 [1·07] by week 313. Similarly, a rapid decline in total CLN2 Clinical Rating Scale score (motor, language, vision, and seizure domains) was observed for historical controls compared with a more gradual decline in treated patients (Figure 1D). Similar results were attained in analyses performed in matched cohorts (see supplemental results; Figures S3-S5).

Data on change from baseline in individual CLN2 Clinical Rating Scale domain scores are shown in Figure S6 and Table S2. Vision domain score was seen to decline in both groups, albeit more rapidly in the historical controls (Figure S6). Treated patients showed a mean decline of 1.4 points from baseline to week 289 compared with a decline of 2.3 points for historical controls (Table S2). The seizure domain score provides an assessment of the frequency of tonic-clonic seizures: mean (SD) seizure domain score increased from 1·7 (1·2) at baseline to 2·4 (0·8) at week 289 in treated patients but decreased from 1·7 (1·1) to 0·7 (1·2) in historical controls, indicating declining frequency of seizures in treated patients and increasing frequency of seizures in historical controls (Table S2 and Figure S6).

Mean percentage change from baseline in total gray matter volume of treated patients, assessed by MRI, is shown in Figure 2. The mean absolute change from baseline to week 49 (end of the primary study) was -9·7%. At week 145, the observed change from baseline was -13·4% and, as of the last observation in the study, the change from baseline was -14·7%.

Data on exploratory efficacy endpoints (mortality [Figure S7], quality of life [Tables S3 and S4], and developmental milestones [Table S5]) are presented in the Supplementary Materials.

All participants experienced at least 1 AE (Table 2 and Table S6). Most AEs were Grade 1 or 2 in severity; 18 participants (75%) had at least one AE of Grade 3 and 3 participants (13%) had a Grade 4 AE. Grade 4 AEs were blindness, pyelonephritis, and status epilepticus. Fifteen participants experienced 52 AEs leading to dose interruptions; no AEs led to dose reduction. There were no deaths and no study discontinuations because of an AE. A total of 237 AEs in 23 participants were considered related to study drug; the most common drug-related AEs were pyrexia (127 events in 11 participants), hypersensitivity (16 events in 10 participants), seizure (14 events in 9 participants), vomiting (15 events in 6 participants), and epilepsy (4 events in 4 participants).

Overall, 107 serious adverse events (SAEs) were reported in 21 participants (88%) (Table 2 and Table S7). A total of 12 SAEs in 8 participants were considered related to study drug; the most common drug-related SAEs were hypersensitivity (9 events in 7 participants), infusion-associated reaction (2 events in 1 participant), pleocytosis (1 event in 1 participant).

Eighteen participants (75%) had a total of 56 hypersensitivity AEs (HAEs; Table S8); 29 were Grade 1, 19 were Grade 2, and 8 were Grade 3. There were no AEs of anaphylaxis or anaphylactoid reactions according to the criteria of the US National Institute of Allergy and Infectious Diseases. Twenty-one participants (88%) had a combined 79 device-related AEs (Table S9): the most common were device-related infections (15 events in 9 participants) and device end-of-service events, representing prophylactic replacement of the ICV device (13 events in 13 participants). A total of 29 device-related SAEs were reported in 16 participants, including 12 device-related infections in 7 participants. A total of 14 device-related AEs in 7 participants led to ICV device replacement (2 participants had 3 device replacement; 2 participants had 2 replacements, and 3 participants had a single replacement): device-related infection (9 events in 6 participants), device leakage (2 events in 2 participants), device deployment issue (2 events in 2 participants), and device malfunction (1 event in 1 participant). Device-related infections were managed with intravenous antibiotics, with the specific agent used being determined based on the organism identified. In all cases, the ICV device was successfully replaced without complication and without discontinuation of study drug.

A total of 7 participants (29%) experienced 15 cardiovascular events (most common were: bradycardia, 4 events; hypotension, 4 events; hematoma, 2 events) and 23 participants (96%) experienced 693 events mapping to the convulsions Standardized MedDRA Query (Table S10). No events of hydrocephalus, meningitis, or unexpected rapid decline in motor-language score were reported. The proportion of participants who reported ≥1 event of convulsions as an AE declined from 88% (n=21) during weeks 0-24, reaching a nadir of 26% (n=23) during weeks >144 to 168, before increasing to 59% (n=13) in weeks >216 (Figure S8).

The anti-drug antibody (ADA) response in all participants by time on treatment is displayed for CSF TAb (Figure S9A) and serum TAb (Figure S9B). CSF TAb response was detected in 10 participants (42%); earliest time to onset was 13 weeks. CSF TAb titers returned to undetectable levels in 9 out of 10 ADA positive participants by the end of the study. Serum TAb response was detected in 19 participants (79%); titers were sustained in 12/19 (63%), declined in 5/19 (26%), and reverted to undetectable in 2/19 (11%) by the end of the study. Low titer NAb were detected in the CSF of 3 participants (13%) at a single visit. Change from baseline in the combined motor-language score was comparable between CSF TAb-negative and TAb-positive participants (Figure S10). Six participants reported 8 Grade 3 HAEs; however, no association was found between serum ADA titer and either the incidence or severity of HAEs (Figure S11A and S11B, respectively). Serum samples collected from all participants reporting Grade 3 HAEs were tested and found negative for drug-specific IgE.

DISCUSSION

Intracerebroventricular cerliponase alfa is the first disease-modifying treatment approved for CLN2 disease. Treatment with 300 mg cerliponase alfa every other week for at least 96 weeks was shown to result in meaningful preservation of motor and language function, with acceptable safety and tolerability,[7] and cerliponase alfa has increasingly become the standard of care for children with CLN2 disease, where available.[15] In this report, we confirm that slowing of clinical disease progression is maintained through >5 years of treatment, with expected but manageable safety events. After completion of the 240-week treatment period of the study, participants were not required to continue on treatment. However, all who completed the treatment period did indeed continue to receive infusions and remained on treatment at the time of the 6-month safety follow-up visit.

After receiving cerliponase alfa for at least 162 weeks at the 300 mg dose, treated patients were found to be less likely than historical untreated controls to experience an unreversed 2-point decline or a score of 0 in the combined motor-language domains of the CLN2 Clinical Rating Scale. The mean (SD) rate of decline in the combined motor-language domain score was 1·75 points/48 weeks lower for treated patients than for historical controls. Rates of decline were comparable to those reported after 96 weeks of treatment suggesting that attenuation of disease progression is maintained. Although a decline in motor-language score was still seen in treated patients, the attenuation relative to historical controls was clinically meaningful: by the end of study, motor-language score in treated patients had declined by approximately 1.5 points to a median score of 2: at this level children require assistance to walk and have limited language. In comparison, for historical controls, the median time to reach a motor-language score of 0, representing complete loss of ambulation and ability to communicate through speech, was 109 weeks.

Seizures are a predominant feature of CLN2 disease and remain a significant burden throughout disease progression. CLN2 Clinical Rating Scale seizure domain scores indicated a reduction in the frequency of tonic-clonic seizures in treated patients, whereas an increase in frequency was observed in historical controls, suggesting that treatment may also have some benefit on seizures. Consistent with this, the proportion of participants with convulsions AEs declined over time. However, it should be noted that changes in use of antiepileptic drugs, concurrent illnesses, and brain atrophy over disease progression may also affect seizure frequency and severity.

Patients with CLN2 disease suffer from progressive loss of vision and are typically blind by the age of 7-10 years.[11] ICV administration of cerliponase alfa is not expected to have an impact on the retina, and decline in vision accompanied by progressive retinal degradation has been documented in patients receiving treatment.[16] Consistent with this, scores on the vision domain of the CLN2 Clinical Rating Scale were seen to decline in both treated and historical control patients, although the decline was somewhat delayed in treated patients, suggesting that despite the lack of effect on retinal degradation, there may be an impact of treatment on the occipital visual cortex. Studies in canine models of CLN2 disease have demonstrated that intravitreal injection of cerliponase alfa can preserve retinal structure and function[17,18] and clinical trials evaluating the impact of intravitreal cerliponase alfa are ongoing (NCT05152914).

Among treated patients, total gray matter volume declined over the duration of the study. However, most of this decline occurred over the first 49 weeks of treatment, with a smaller incremental loss by week 97, after which little further change was observed. This may suggest that there is an initial loss of cortical gray matter followed by stabilization. Interpretation of these findings is limited by the lack of comparator data for historical untreated controls. However, Loebel et al. have shown progressive loss of supratentorial cortical gray matter (up to 12·5 % per year) in a longitudinal cohort of untreated CLN2 disease patients.[13]

Time to death was evaluated as an exploratory outcome in the study. Median age of death for historical untreated controls was 10·4 years; none of the treated patients died during the study. In CLN2 disease, symptomatic care (e.g., mechanical ventilation, gastrostomy tube feeding) may prolong life, but such measures do not generally alter disease progression and thus prolongation of life may be predominantly in the most progressed stages of disease. Supportive analyses of the primary efficacy endpoint demonstrating a delay in time to reach a score of zero suggest that the increased survival observed in patients treated with cerliponase alfa is accompanied by preservation of function. Assessments of quality of life and achievement of developmental milestones were also considered as exploratory efficacy endpoints in the study. Quality of life scores showed a substantial impairment at study baseline, reflecting the burden of disease and extent of progression in these patients at the time of enrollment. Scores in PedsQL domains relating to physical, social and school functioning were lower at end of study compared to baseline, while the others were minimally changed or higher. Interpretation of the significance of these changes is limited by the lack of comparator data from historical controls as well as the lack of defined, population-specific clinically important difference estimates. Moreover, the high degree of variability seen suggests the need to evaluate these outcomes at the patient level and in the context of disease progression and intercurrent events.

~~however the lack of comparator data from historical control patients as well as the lack of defined, population-specific clinically important difference estimates limits the interpretation of the changes observed.~~

The safety profile of ICV cerliponase alfa was similar to that observed after 96 weeks. The most common SAEs reflect treatment with an exogenous protein and complications arising from use of the ICV device. All participants who experienced Grade 3 hypersensitivity reactions tested negative for the presence of drug-specific IgE antibodies, a hallmark of acute type I hypersensitivity reactions.[19-21] The impact of immunogenicity on safety and efficacy was consistent with previously reported findings based on up to 129 weeks of treatment.[9]

All participants who experienced ICV device-related infections, or who required replacement of the device for other reasons, continued therapy after removal of the device, intravenous antibiotic treatment when appropriate, and subsequent device replacement. The occurrence of device-related infections emphasizes the importance of strict adherence to sterile technique at all times when preparing and administering cerliponase alfa.[22,23] In addition to ICV device replacement following infections or complications, replacement is recommended prior to 4 years of use due to the potential for material degradation.[24] Participants in this study had received treatment for approximately 5 years by its conclusion and more than half were observed to have had a prophylactic device replacement.

The major limitation of both the primary and extension studies is its open-label, non-randomized design and lack of a contemporaneous control group. The natural history cohort had less frequent assessments and a substantially longer epoch of assessment than the treatment group. Bias could arise if changing standard of care had an impact on motor-language assessment in the control group. We note, however, that the natural history database is the largest available and that the duration of follow-up for both natural history patients and treated patients was substantial. To limit the likelihood that findings were the result of bias, a number of supportive analyses were conducted, including patient-level matching and covariate adjustments. All such analyses confirmed the observed treatment benefit, however the potential for unmeasured confounding cannot be excluded. Additionally, for analyses of survival and time to loss of function (motor-language score 0) where few events were observed in treated patients, length of follow-up time is a limitation and ~~.~~ although penalization methods were used for analyses, sparse-data bias may remain.[25] The motor-language score itself has inherent limitations in that it does not capture many important aspects of CLN2 disease and, moreover, lacks granularity with domain scores covering a comparatively wide range of abilities. However, it was selected as the primary efficacy outcome in this study because it provided an objective assessment that could be used to compare outcomes in treated patients with those of historical controls.

In conclusion, data from this study demonstrate that long-term ICV administration of cerliponase alfa in children with CLN2 disease slows decline in critical motor and language function compared with untreated historical controls. Although long-term cerliponase alfa treatment is associated with treatment-related complications, these were manageable and did not result in treatment discontinuation. A further study in an expanded cohort including children younger than 3 years of age (NCT02678689) will explore outcomes following initiation of cerliponase alfa treatment in presymptomatic children.[26]

Contributions

All authors made substantial contributions to the acquisition and interpretation of study data; revised the manuscript critically for important intellectual content; approved the final version to be published; and are accountable for all aspects of the work. PS conducted the data analyses with consultation from JCP. All the authors vouch for the accuracy and completeness of the

study results, adherence to the protocol, and reporting of AEs. The corresponding author (AS) and sponsor authors directly accessed the study data. All authors had full access, if requested, to all the data in the study and accept responsibility to submit for publication. The manuscript was drafted by a medical writer (Abigail Hunt, an employee of BioMarin) under the direction of the authors.

Declaration of interests

AS and MN have received payments to their institution as a study site according to clinical trial budget, medical writing support, honoraria and travel support from BioMarin Pharmaceutical Inc; EDLR has received salary support as the primary investigator and salary support for the research personnel, honoraria and travel support from BioMarin Pharmaceutical Inc and consulting fees from Zogenix; NS has received consulting fees from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB, Takeda, and Angeun; honoraria from BioMarin Pharmaceutical Inc, JAZZ Pharma, UCB and Zogenix; and travel fees BioMarin Pharmaceutical Inc and Jazz Pharma; PG has received payments to his institution as a study site according to clinical trial budget, honoraria and travel support from BioMarin Pharmaceutical Inc; MT has received honoraria from BioMarin Pharmaceutical Inc; SCA has received research salary support from BioMarin Pharmaceutical Inc, research effort support for study on erenumab from Amgen, research effort support for study on Rimegepant from Pfizer, grant support for fellowship training from NINDS/Neuronext and honoraria as associate editor from Pediatric Neurology; DJB and JPD have received contractor fees paid by BioMarin Pharmaceutical Inc for analyzing imaging data that appears in the paper; PS is an employee and stockholder of BioMarin Pharmaceutical Inc; SB and ACherukuri are employees of BioMarin Pharmaceutical Inc; JLCP is an employee & stockholder of BioMarin Pharmaceutical Inc and a scientific advisor for NPKUA; ~~PG~~ AChakrapani, CS, EW, and LMW reported no conflicts of interest.

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Data sharing

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes.

Additional supporting documents may be available upon request.

Investigators will be able to request access to these data and supporting documents via a data sharing portal beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of relevant product.

Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology.

Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com/patients/publication-data-request/ to determine whether access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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Figure Legends

Figure 1: CLN2 Clinical Rating Scale Outcomes
Panels A and B show Kaplan-Meier curves for time to unreversed 2-point decline from baseline or a score of 0 (Panel A), and time to unreversed score of 0 (Panel B) in the combined score for motor and language domains. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Panels C and D show change from baseline in the score for motor and language function (Panel C) and in the score for all four domains of the CLN2 Rating Scale (motor, language, vision, and seizure domains; Panel D) for treated patients and historical controls. Error bars indicate 95% confidence intervals.

Figure 2: Change from Baseline in Total Gray Matter Volume among Treated Patients
Graph shows the percent change from baseline in total gray matter volume among treated patients. Error bars represent 95% confidence intervals. Baseline was defined as the last observation before the first 300 mg dose of cerliponase alfa. Numbers shown on the figure represent the number of patients with available data at each time point.

References

1. Chang M, Cooper JD, Davidson BL, et al. CLN2. In: Mole SE, Williams Re, Goebel HH, eds. The Neuronal Ceroid Lipofuscinoses (Batten Disease). 2nd ed; 2011: 80-109.
2. Sleat DE, Gin RM, Sohar I, et al. Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. *Am J Hum Genet* 1999; **64**(6): 1511-23.
3. Fietz M, AlSayed M, Burke D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. *Mol Genet Metab* 2016; **119**(1-2): 160-7.
4. Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. *Lancet Child Adolesc Health* 2018; **2**(8): 582-90.
5. Kohlschutter A, Schulz A. CLN2 Disease (Classic Late Infantile Neuronal Ceroid Lipofuscinosis). *Pediatr Endocrinol Rev* 2016; **13 Suppl 1**: 682-8.
6. Schulz A, Kohlschutter A, Mink J, Simonati A, Williams R. NCL diseases - clinical perspectives. *Biochim Biophys Acta* 2013; **1832**(11): 1801-6.
7. Schulz A, Ajayi T, Specchio N, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. *N Engl J Med* 2018; **378**(20): 1898-907.
8. Schulz A, Simonati A, Laine M, Williams R, Kohlschutter A, Nickel M. The DEM-CHILD NCL Patient Database: A tool for the evaluation of therapies in neuronal ceroid lipofuscinoses (NCL). *European Journal of Pediatric Neurology* 2015; **19**: S16.
9. Cherukuri A, Cahan H, de Hart G, et al. Immunogenicity to cerliponase alfa intracerebroventricular enzyme replacement therapy for CLN2 disease: Results from a Phase 1/2 study. *Clin Immunol* 2018; **197**: 68-76.
10. Wyrwich KW, Schulz A, Nickel M, et al. An adapted clinical measurement tool for the key symptoms of CLN2 disease. *Journal of Inborn Errors of Metabolism and Screening* 2018; **6**: 1-7.
11. Steinfeld R, Heim P, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. *Am J Med Genet* 2002; **112**(4): 347-54.
12. Worgall S, Kekatpure MV, Heier L, et al. Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. *Neurology* 2007; **69**(6): 521-35.
13. Lobel U, Sedlacik J, Nickel M, et al. Volumetric Description of Brain Atrophy in Neuronal Ceroid Lipofuscinosis 2: Supratentorial Gray Matter Shows Uniform Disease Progression. *AJNR Am J Neuroradiol* 2016; **37**(10): 1938-43.
14. Ru Y, Corado C, Soon RK, Jr., et al. Neurofilament light is a treatment-responsive biomarker in CLN2 disease. *Ann Clin Transl Neurol* 2019; **6**(12): 2437-47.
15. Mole SE, Schulz A, Badoe E, et al. Guidelines on the diagnosis, clinical assessments, treatment and management for CLN2 disease patients. *Orphanet J Rare Dis* 2021; **16**(1): 185.
16. Dulz S, Schwering C, Wildner J, et al. Ongoing retinal degeneration despite intraventricular enzyme replacement therapy with cerliponase alfa in late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2 disease). *Br J Ophthalmol* 2022.
17. Whiting REH, Pearce JW, Vansteenkiste DP, et al. Intravitreal enzyme replacement preserves retinal structure and function in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **197**: 108130.

18. Whiting REH, Robinson Kick G, Ota-Kuroki J, et al. Intravitreal enzyme replacement inhibits progression of retinal degeneration in canine CLN2 neuronal ceroid lipofuscinosis. *Exp Eye Res* 2020; **198**: 108135.
19. de Las Vecillas Sanchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug Hypersensitivity and Desensitizations: Mechanisms and New Approaches. *Int J Mol Sci* 2017; **18**(6).
20. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. *Am Fam Physician* 2003; **68**(9): 1781-90.
21. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011; **127**(3 Suppl): S67-73.
22. de Los Reyes E, Lehwald L, Augustine EF, et al. Intracerebroventricular Cerliponase Alfa for Neuronal Ceroid Lipofuscinosis Type 2 Disease: Clinical Practice Considerations From US Clinics. *Pediatr Neurol* 2020; **110**: 64-70.
23. Schwering C, Kammler G, Wibbeler E, et al. Development of the "Hamburg Best Practice Guidelines for ICV-Enzyme Replacement therapy (ERT) in CLN2 Disease" Based on 6 Years Treatment Experience in 48 Patients. *J Child Neurol* 2021; **36**(8): 635-41.
24. Inc. BP. Prescribing Information: BRINEURA (cerliponase alfa) injection, for intraventricular use. 2020.
25. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016; **352**: i1981.
26. Schulz A, de Los Reyes E, Specchio N, et al. Cerliponase alfa for the treatment of CLN2 disease in an expanded patient cohort including children younger than three years: Interim results from an ongoing clinical study. *Mol Genet Metab* 2021; **132**(2): S95.

626 **Table 1. Demographic and Clinical Characteristics of Participants at Baseline (Safety Population)***

	Participants (n=24)
Age at enrollment, years	
Mean (SD)	4·9 (1·28)
Median (IQR)	4·6 (4.0, 5.5)
Range	3·1, 8·9
Sex, n (%)	
Male	9 (38)
Female	15 (63)
Race, n (%)	
Asian	1 (4)
Black	0
White	23 (96)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	1 (4)
Not Hispanic or Latino	23 (96)
Baseline motor/language CLN2 Rating Scale score†	
Mean (SD)	3·5 (1·2)
Median (IQR)	3·0 (3.0, 4.0)
Score, n (%)	
6	2 (8)
5	2 (8)
4	6 (25)
3	11 (46)
2	2 (8)
1	1 (4)
Genotype, n (%)	
2 common alleles‡	9 (38)
1 common and 1 uncommon allele§	8 (33)
2 uncommon alleles	7 (29)

* Percentages may not sum to 100 as a result of rounding
† Score was assessed just prior to first 300 mg dose; higher scores represent higher functioning
‡ Common alleles are c.622C>T and c.509-1G>C
§ Uncommon alleles were c.1448G>A, c.380G>A, c.833A>G, c.1015C>T, c.731T>C, c230-13T>A c.1261T>A, and c.1087delinsTT

SD, standard deviation; IQR, interquartile range

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628 **Table 2: Adverse Events: Safety Population**

	Participants (n=24) 629
Common adverse events, n (%)	
Upper respiratory tract infection	21 (88)
Pyrexia	20 (83)
Viral upper respiratory tract infection	19 (79)
Vomiting	19 (79)
Generalized tonic-clonic seizure	16 (67)
Seizure	14 (58)
Constipation	13 (54)
Device end of service	13 (54)
Dysphagia	13 (54)
Epilepsy	13 (54)
Rhinitis	13 (54)
Gait disturbance	12 (50)
Cough	11 (46)
Dystonia	11 (46)
Tremor	11 (46)
Visual impairmemt	11 (46)
Hypersensitivity	10 (42)
Myoclonus	10 (42)
Device-related infection	9 (38)
Diarrhoea	9 (38)
Extensor plantar response	9 (38)
Gastroenteritis	9 (38)
Needle issue	9 (38)
Sleep disorder	9 (38)
Viral infection	9 (38)
Serious adverse events, n (%)	
Any serious adverse event	21 (88)
Device end of service	13 (54)
Hypersensitivity	7 (29)
Device-related infection	7 (29)
Upper respiratory tract infection	5 (21)
Dysphagia	4 (17)
Gastroenteritis	4 (17)
Pleocytosis	3 (13)
Dental caries	2 (8)
Device deployment issue*	2 (8)
Epilepsy	2 (8)
Pharyngitis bacterial	2 (8)
Pyelonephritis	2 (8)
Pyrexia	2 (8)

Common adverse events shown are those reported in more than 35% of the participants.
Serious adverse events shown are those reported in more than 1 participant.
*Device deployment issues included procedural issues during the placement or positioning of the intracerebroventricular device.

Figure 1

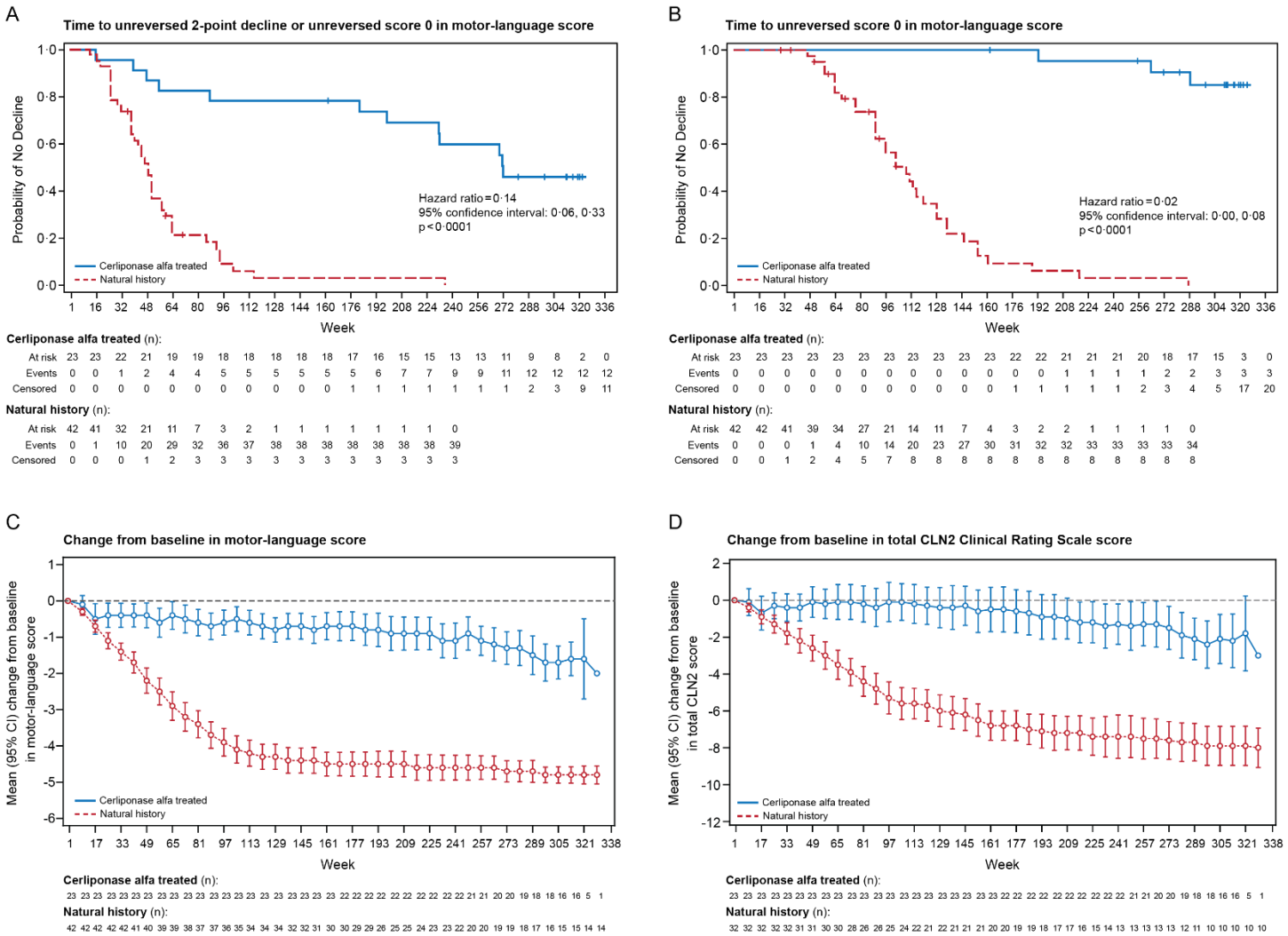
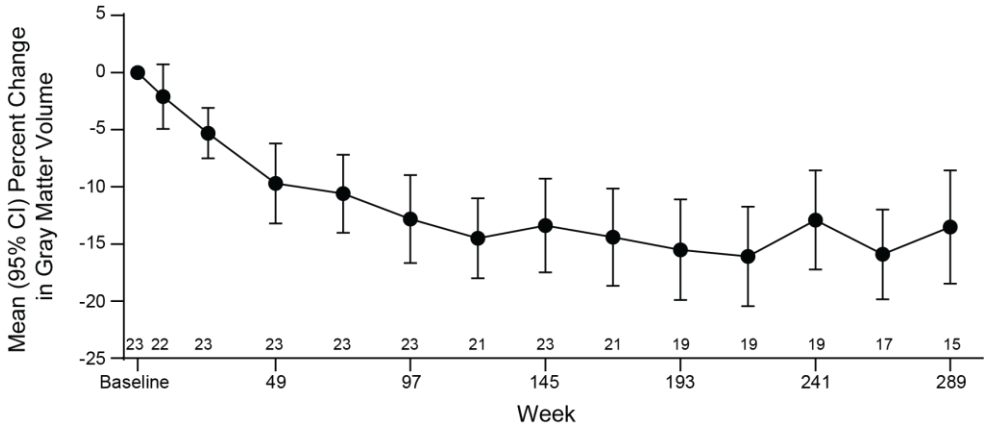

A
Time to unreversed 2-point decline or unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·14
95% confidence interval: 0·06, 0·33
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 22 21 19 19 18 18 18 18 18 17 16 15 15 13 13 11 9 8 2 0
Events 0 0 1 2 4 4 5 5 5 5 5 5 6 7 7 9 9 11 12 12 12 12
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 2 3 9 11
Natural history (n):
At risk 42 41 32 21 11 7 3 2 1 1 1 1 1 1 1 0
Events 0 1 10 20 29 32 36 37 38 38 38 38 38 38 38 39
Censored 0 0 0 1 2 3 3 3 3 3 3 3 3 3 3 3
B
Time to unreversed score 0 in motor-language score
Probability of No Decline
Hazard ratio = 0·02
95% confidence interval: 0·00, 0·08
p < 0·0001
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
At risk 23 23 23 23 23 23 23 23 23 23 23 22 22 21 21 21 20 18 17 15 3 0
Events 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 2 2 3 3 3
Censored 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 2 3 4 5 17 20
Natural history (n):
At risk 42 42 41 39 34 27 21 14 11 7 4 3 2 2 1 1 1 1 0
Events 0 0 0 1 4 10 14 20 23 27 30 31 32 32 33 33 33 33 34
Censored 0 0 1 2 4 5 7 8 8 8 8 8 8 8 8 8 8 8 8
C
Change from baseline in motor-language score
Mean (95% CI) change from baseline in motor-language score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 18 18 16 16 5 1
Natural history (n):
42 42 42 42 42 41 40 39 39 38 37 37 36 35 34 34 34 32 32 31 30 30 29 29 26 25 25 24 23 23 22 20 20 19 19 18 17 16 15 15 14 14
D
Change from baseline in total CLN2 Clinical Rating Scale score
Mean (95% CI) change from baseline in total CLN2 score
Cerliponase alfa treated
Natural history
Week
Cerliponase alfa treated (n):
23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 22 22 22 22 22 22 21 21 20 20 19 19 18 18 16 16 5 1
Natural history (n):
32 32 32 32 32 31 31 30 30 30 28 26 26 25 24 22 21 22 21 21 21 20 20 19 19 18 17 17 16 15 14 13 13 13 13 13 12 11 10 10 10 10 10

Figure 2



Gray Matter Volume	Baseline	49 weeks	97 weeks	145 weeks	193 weeks	241 weeks	289 weeks
Mean (SD) volume, cm^3	452·0 (87·7)	408·3 (88·5)	394·6 (89·3)	390·3 (84·3)	374·2 (89·9)	390·4 (78·4)	371·9 (54·6)
Mean % change from Baseline	-	-10%	-13%	-13%	-16%	-13%	-14%
Annualized % change from Baseline	-	-11%	-14%	-15%	-17%	-14%	-15%
Annualized interval % change	-	-11%	-4%	-1%	-3%	+2%	+1%