ORIGINAL ARTICLE

Study of Intraventricular Cerliponase Alfa for CLN2 Disease

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ABSTRACT

BACKGROUND

Recombinant human tripeptidyl peptidase 1 (cerliponase alfa) is an enzyme-replacement therapy that has been developed to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a rare lysosomal disorder that causes progressive dementia in children.

METHODS

In a multicenter, open-label study, we evaluated the effect of intraventricular infusion of cerliponase alfa every 2 weeks in children with CLN2 disease who were between the ages of 3 and 16 years. Treatment was initiated at a dose of 30 mg, 100 mg, or 300 mg; all the patients then received the 300-mg dose for at least 96 weeks. The primary outcome 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. We also compared the rate of decline in the motor–language score 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).

RESULTS

Twenty-four patients were enrolled, 23 of whom constituted the efficacy population. The median time until a 2-point decline in the motor–language score was not reached for treated patients 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 patients and 2.12±0.98 points in 42 historical controls (mean difference, 1.85; P<0.001). Common adverse events included convulsions, pyrexia, vomiting, hypersensitivity reactions, and failure of the intraventricular device. In 2 patients, infections developed in the intraventricular device that was used to administer the infusion, which required antibiotic treatment and device replacement.

CONCLUSIONS

Intraventricular infusion of cerliponase alfa in patients with CLN2 disease resulted in less decline in motor and language function than that in historical controls. Serious adverse events included failure of the intraventricular device and device-related infections. (Funded by BioMarin Pharmaceutical and others; CLN2 ClinicalTrials.gov numbers, NCT01907087 and NCT02485899.)

Neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a form of Batten's disease, is a rare, autosomal recessive, pediatric neurodegenerative disease resulting from pathogenic variants in the gene encoding lysosomal enzyme tripeptidyl peptidase 1 (*TPP1*).[1,2] A deficiency of TPP1 results in accumulation of lysosomal storage material that causes degenerative changes in neurons throughout the central nervous system and retina.[3] Affected children are functionally normal until the age of 2 to 4 years and subsequently have seizures and delayed language acquisition followed by a rapid decline in motor, language, cognitive, and visual function over a period of 4 to 6 years and death by early adolescence.[4,5] There has been no approved therapy for this disorder.

Natural-history cohorts of children with CLN2 disease have shown progressive decline in motor and language function.[6-8] A database of children with the disease has characterized disease severity and progression with a disease-specific clinical rating scale, including motor, language, and visual function, and incorporates the frequency of grand mal seizures.[9] Specific disease genotypes do not consistently correlate with phenotype, although pathologic variants other than the two most common ones (c.622C→T nonsense mutation and c.509-1G→C splice defect) may be associated with an increased probability of a later onset of the disease.[10]

Cerliponase alfa, a recombinant proenzyme (also called zymogen) form of human TPP1, is an enzyme-replacement therapy that has potential use in patients with CLN2 disease. The administration of enzyme into the ventricular cerebrospinal fluid of young dogs that were spontaneously homozygous for TPP1 deficiency resulted in widespread distribution and uptake in the brain, clearance of lysosomal storage material, preservation of neuronal morphologic features, and a reduction in brain inflammation.[11,12] The treated dogs also had delayed onset and slower progression of neurologic signs and brain atrophy, preserved cognitive function, and an extended life span in a dose-dependent manner.[11,13,14] These findings led to this clinical study of recombinant human TPP1 administered by intraventricular infusion in children with CLN2 disease.

METHODS

STUDY DESIGN AND OVERSIGHT

We performed the open-label study from September 2013 through November 2015 at five centers (one each in Germany, Italy, and the United States and two in the United Kingdom) to assess the efficacy and safety of intraventricular cerliponase alfa in children with CLN2 disease. Written informed consent from a parent or legal guardian of each patient was obtained, and assent was obtained from the patient, if appropriate. The studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by the relevant ethics boards and is available with the full text of this article at NEJM.org.

The study was designed and funded and data were analyzed by the sponsor, BioMarin Pharmaceutical. Assistance with manuscript preparation was provided by a medical writer who was paid by the sponsor, with review by the authors. All the authors vouch for the accuracy and completeness of the study results, adherence to the protocol, and reporting of adverse events.

STUDY PATIENTS

Eligible patients were between the ages of 3 and 16 years and had received a diagnosis of CLN2 disease. All the patients had a combined score of 3 to 6 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 for each of the two domains)[6,7] (Fig. 1) and a score of at least 1 in each of the two domains at screening. Exclusion criteria included the presence of another inherited neurologic disease or illness that might have caused cognitive decline; previous stem-cell therapy, gene therapy, or enzyme-replacement therapy for CLN2 disease; contraindications for neurosurgery or for magnetic resonance imaging (MRI); generalized motor status epilepticus or severe infection within 4 weeks before the initiation of treatment; and known hypersensitivity to any component of the study drug. Patients were referred to study centers by their diagnosing physicians; all the patients who were screened for eligibility were enrolled.

Patients who completed the 48-week open-label study with a score of more than 0 on the

Score	Functional Description	
	Motor Domain	Language Domain
3	Has grossly normal gait; no prominent ataxia, no pathologic falls	Has apparently normal language that is intelligible and grossly age-appropriate, with no decline noted
2	Has independent gait as defined by ability to walk without support for 10 steps; obvious instability and possibly intermittent falls	Has language that has recognizable abnormalities but includes some intelligible words; may form short sentences to convey concepts, requests, or needs
1	Requires external assistance to walk or can only crawl	Has language that is hard to understand with few intelligible words
0	Can no longer walk or crawl	Has no intelligible words or vocalizations

Figure 1. Scoring for Motor and Language Function on the CLN2 Clinical Rating Scale.

The primary end point of the study was an aggregate score in the domains for motor and language function on the CLN2 Clinical Rating Scale. Each domain is scored from 0 (no function) to 3 (normal function) for a maximal possible score of 6 for the two domains.

CLN2 Clinical Rating Scale were eligible to enroll in a 240-week extension study of 300 mg of intraventricular cerliponase alfa administered every 2 weeks (ClinicalTrials.gov number, NCT02485899). Data from the extension study through November 1, 2016, are included in this report.

Patients who were enrolled in the Dementia in Childhood database, which includes children in whom CLN2 disease has been diagnosed in Hamburg, Germany, and Verona, Italy,[9] served as a historical control group. (Details regarding the inclusion criteria for the historical control group are provided in the Supplementary Appendix, available at NEJM.org.)

TREATMENT

An Ommaya or Rickham ventricular reservoir was surgically implanted, with the reservoir placed under the scalp and the catheter placed in the cerebral lateral ventricle in each patient, with placement confirmed on MRI. Cerliponase alfa was administered by means of intraventricular infusion at a rate of 2.5 ml per hour for 4 hours. An antihistamine drug was administered approximately 30 minutes before each infusion.

We conducted a dose-escalation phase in which the study drug was initiated at 30 mg, 100 mg, or 300 mg every 2 weeks, a regimen that was intended to establish an acceptable side-effect profile. During the dose-escalation phase, patients received at least two infusions at each dose level; 3 patients who started at 30 mg received two to six doses, 3 patients who started at 100 mg received two to five doses, and 4 patients who started at 300 mg received one to three doses. This phase was followed by a 48-week period in which the patients received a stable dose of 300 mg every 2 weeks. Details regarding the study design are provided in Figure S1 in the Supplementary Appendix.

At the parents' request, one patient dropped out of the study after the receipt of one dose of the study drug owing to an unwillingness to continue with study visits and procedures; this patient was not included in the efficacy analysis but was included in the safety analysis. A data and safety monitoring committee approved the dose escalations. (Details are provided in the Supplementary Appendix.)

OUTCOME MEASURES

The primary efficacy outcome was the time until the first unreversed 2-point decline in the score on the CLN2 Clinical Rating Scale measuring motor and language skills or until the attainment of a combined motor–language score of 0, as compared with the time in the historical control group. The same analysis was performed for the language score and motor score individually. The performance was assessed over a period of at least 96 weeks during which patients received the 300-mg dose of cerliponase alfa in both the primary and the extension studies. We also compared the absolute scores with those in matched historical controls, along with scores on an extended CLN2 scale in four domains — motor skills, language, vision, and seizure — that ranges from 0 to 12, with 0 indicating no function and 3 representing normal function in each

of the four domains (Table S1 in the Supplementary Appendix).

Trained raters administered the clinical rating scales in a standardized manner. Brain gray-matter volumes were measured with the use of high-resolution MRI. Data regarding adverse events and concomitant medications were reported at every visit. The attribution of adverse events to cerliponase alfa were determined by the site investigator and were not adjudicated. (Details regarding these data, including the timing of visits during the infusion, dose escalation, and stable dose periods, are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

All the patients who had received more than one dose of cerliponase alfa were included in all the efficacy analyses. Study patients were compared with a historical control group of 42 patients, who were selected from 69 patients in the CLN2 database after the exclusion of 27 patients (1 twin of a historical control, 7 patients who later enrolled in the treatment study, 17 patients who lacked sufficient data regarding scores on the motor and language scale, and 2 patients who did not meet clinical criteria) (see the Supplementary Appendix). The baseline measurement was the last observation preceding the first administration of 300 mg of cerliponase alfa. Safety results are relative to the last observation preceding device implantation. Among patients in the historical control cohort, baseline scores on the motor and language scale were defined as the first score of less than 6 at the age of 36 months or more; the baseline age of assessment was the midpoint of the age range of assessments at the time this score was obtained.

For the primary efficacy outcome, we calculated the rate of decline in the motor–language score as the change 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). The mean rate of decline on the motor–language score was compared with the use of a two-sample t-test with Satterthwaite's approximation to accommodate unequal variances and was estimated by analysis of covariance after adjustment for baseline variables (motor–language score, age, genotype, and sex). We used Kaplan–Meier methods and a Cox proportional-hazards model to compare the time until the primary outcome, after adjustment for the baseline motor–language score, motor score alone, language score alone, age, genotype, and sex.

We compared the change from baseline in the total CLN2 score on the four-domain scale (range, 0 to 12) between treated patients and 1:1 matched patients in the historical control group who had the closest values with respect to the baseline motor–language score, age (within 3 months), and genotype (equal number of common alleles c.622C→T and c.509-1G→C).[10] We performed a sensitivity analysis in which we matched one treated patient with many historical controls to confirm the robustness of the results (see the Supplementary Appendix). Changes from baseline in MRI measurement of gray-matter volume were summarized descriptively.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The efficacy population consisted of 23 patients, all of whom continued to participate in the extension study. The demographic and clinical characteristics of the patients are summarized in Table 1. At the time of screening, most of the patients were at the lower boundary of the combined motor–language score for inclusion in the study; 20 of the patients had a combined motor–language score of 3 or 4 out of 6, and the median score among all the patients was 3. By the time of the initiation of the regimen of 300 mg of cerliponase alfa, the patients' scores ranged from 1 to 6 (median, 3).

In the matched comparison between study patients and historical controls, six study patients could not be matched according to all three prespecified criteria with any of the children in the control group, which resulted in 17 matched pairs of patients for the analysis.

ADMINISTRATION OF STUDY DRUG

The mean (±SD) duration of treatment with any dose of cerliponase alfa was 117±33 weeks (range, 1 to 161); the mean duration at the 300-mg dose was 115±30 weeks (range, 1 to 145). All the patients in the efficacy population received at least 96 weeks of treatment at the 300-mg dose and received 99% of all planned doses.

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

Characteristic	Patients (N=24)
Age at enrollment — mo	
Mean	60±15
Median (range)	58 (40–108)
Sex — no. (%)	
Male	9 (38)
Female	15 (62)
Result on rating of motor and language function†	
Mean score	3.7±1.0
Score — no. (%)	
6	2 (8)
5	2 (8)
4	7 (29)
3	13 (54)
2	0
1	0
Genotype — no. (%)	
Two common alleles‡	9 (38)
One common and one uncommon allele	8 (33)
Two uncommon alleles	7 (29)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Higher scores represent higher functioning. Among the 23 patients in the efficacy population (after the withdrawal of 1 patient from the safety population), the mean score at baseline was 3.5±1.2; the score was 6 in 9% of the patients, 5 in 9%, 4 in 22%, 3 in 48%, 2 in 9%, and 1 in 4%.
‡ The common alleles are c.622C→T and c.509-1G→C.

Figure 2 (facing page). Time until the First 2-Point Decline on the CLN2 Clinical Rating Scale.

Shown are Kaplan–Meier curves for the time until the primary efficacy outcome, which was defined as an unreversed decrease from baseline of 2 or more points in the combined score for motor and language function or a combined score of 0 on the CLN2 Clinical Rating Scale. The same analysis was performed for the language score and motor score individually. Baseline was defined as the last observation before the initiation of a 300-mg regimen of cerliponase alfa. After adjustment for baseline scores on the rating scale (for combined motor and language function, motor function, and language function), age, genotype, and sex, patients who received the study drug were significantly less likely than those in the historical control group to have the primary efficacy outcome for combined motor and language function (Panel A), for motor function alone (Panel B), and for language function alone (Panel C). Tick marks indicate censoring of data.

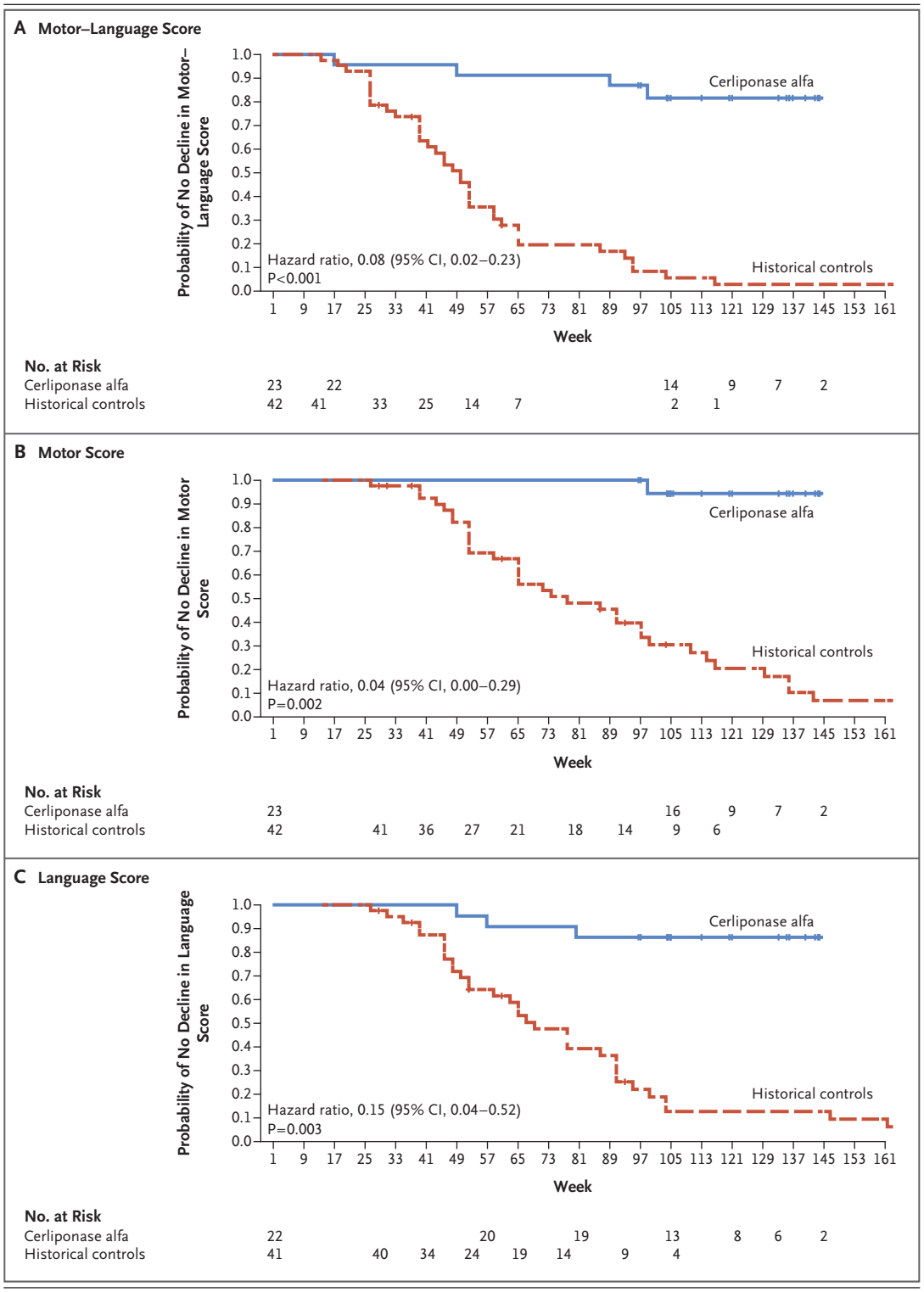
OUTCOMES

Treated patients were less likely than historical controls to have an unreversed 2-point decline in the combined motor–language score (hazard ratio, 0.08; 95% confidence interval [CI], 0.02 to 0.23; P<0.001), as well as in the motor score alone (hazard ratio, 0.04; 95% CI, 0.00 to 0.29; P=0.002) and in the language score alone (hazard ratio, 0.15; 95% CI, 0.04 to 0.52; P=0.003) (Fig. 2). The median time until a 2-point decline in the score on the motor–language scale was not reached among the treated patients and was 345 days (49.3 weeks) among the historical controls; 9% of the treated patients had a decline of 2 points at 345 days.

The unadjusted mean rate of decline in the score on the motor–language scale per 48-week period was 0.27±0.35 points among the 23 treated patients as compared with 2.12±0.98 among the 42 historical controls, a difference of 1.85±0.21 points (95% CI, 1.51 to 2.18; P<0.001). After adjustment for the baseline covariates (age, motor–language score, and genotype), the rate of decline was 0.38±0.10 points among the treated patients and 2.06±0.15 among the historical controls, a mean difference of 1.68 points (95% CI, 1.29 to 2.06; P<0.001).

In the comparison of 17 matched pairs of children, the treated patients had a mean decrease from baseline in the motor–language score of 0.20±0.67 points after 48 weeks of treatment, as compared with a decrease of 1.90±1.23 points among the historical controls during the same period (Fig. 3A). After 96 weeks, the mean decrease in the motor–language score was 0.50±0.71 points among the treated patients and 2.80±1.10 points among the historical controls. Two of the treated patients who had a baseline motor–language score of 6 did not lose a point during the study period.

On the total four-domain scale, the treated patients had a mean increase of 0.30±1.70 points, as compared with a decrease of 2.80±2.04 points in the historical controls, after 48 weeks of treatment (Fig. 3B). After 96 weeks, the mean increase in the total score among treated patients was 0.40±2.08 points, as compared with a decrease of 4.30±2.26 points among the historical controls. Between-group differences for the



entire set of matched comparisons are provided in Figure S4 in the Supplementary Appendix.

In the treatment group, the mean percent change in gray-matter volume was a decrease of 12.4±9.2% from baseline to 96 weeks, which represented an annualized decrease of 6.7%

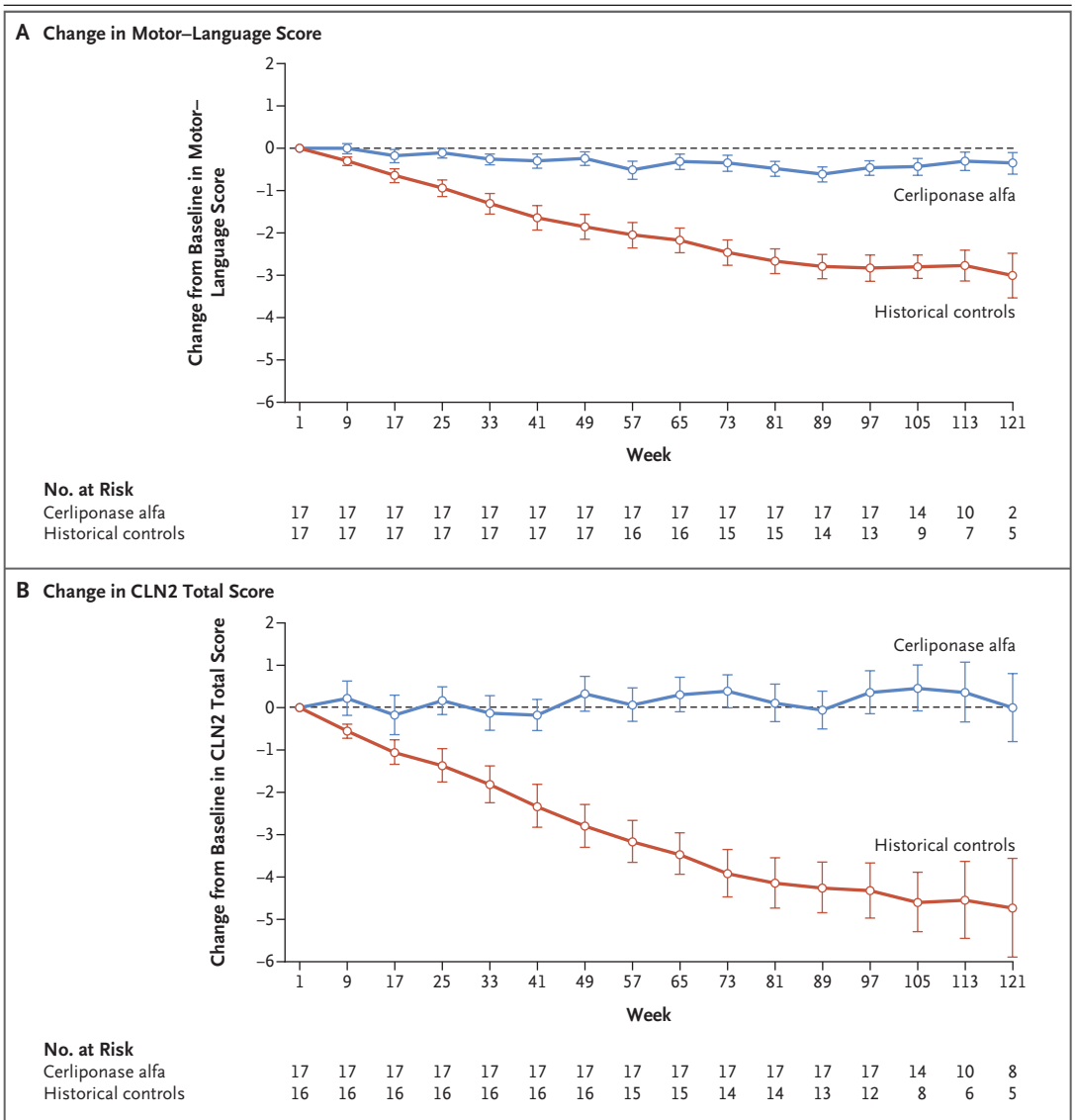


Figure 3. Mean Change from Baseline in Two-Domain and Four-Domain Scores in Matched Comparisons with Historical Controls.

Shown is the change from baseline in the score for motor and language function (Panel A) and in the score for all four domains of the CLN2 Rating Scale (motor, language, vision, and seizure domains) (Panel B) in the two matched study groups. At 49 weeks, the mean change from baseline in the combined score for motor and language function was −0.2 among treated patients and −1.9 among historical controls; at 97 weeks, the mean change was −0.5 and −2.8, respectively. At 49 weeks, the mean change from baseline in the four-domain score was 0.3 among treated patients and −2.8 among historical controls; at 97 weeks, the mean change was 0.4 and −4.3, respectively. The I bars indicate standard errors.

(a decrease of 10.5% in the first year and 3.3% in the second year) (Fig. S5 in the Supplementary Appendix). The rate of change in gray-matter volume was not measured in the control group.

ADVERSE EVENTS

The safety population consisted of 24 patients, including 1 patient who had dropped out after only one dose of the study drug because of an unwillingness to continue with study visits and

procedures. There were no deaths and no study discontinuations because of an adverse event. The treatment of device-related infections resulted in treatment delays in 2 patients (8%). All the patients had at least one adverse event (Table 2, and Table S4 in the Supplementary Appendix). The most common adverse events were convulsions (96%), pyrexia (71%), vomiting (63%), hypersensitivity reactions (63%), upper respiratory tract infection (54%), and nasopharyngitis and rhinitis (42% each). Ten patients (42%) had an adverse event with a maximum severity of grade 1 or 2; 14 patients (58%) had at least one adverse event of grade 3 or higher. There was one serious grade 4 adverse event of unprovoked status epilepticus, which occurred 7 days after the last infusion and lasted for 45 minutes.

Among the 55 serious adverse events that were reported in 20 patients (83%), 11 were considered by investigators to be related to either the study drug or the intraventricular device (Table 2, and Table S5 in the Supplementary Appendix). The most common serious adverse events were hypersensitivity (29%), upper respiratory tract infection (21%), epilepsy (17%), pharyngitis (17%), gastroenteritis (13%), pyrexia (8%), and device-related infection (8%). All the adverse events resolved spontaneously or with appropriate medical management, which allowed for subsequent administration of the study drug.

Fifteen patients (63%) had a total of 37 hypersensitivity adverse events, most of which were of grade 1 or 2 (Table S6 in the Supplementary Appendix). The 8 patients who had a serious or grade 3 hypersensitivity adverse event had negative results on testing for serum drug-specific IgE. There were no adverse events of anaphylaxis or anaphylactoid reactions, according to the criteria of the National Institute of Allergy and Infectious Diseases.

Twelve patients (50%) had 34 device-related adverse events, of which 5 events were of grade 3 in 4 patients (Table S7 in the Supplementary Appendix). Three of these events were device-related infections that were detected on monitoring of cerebrospinal fluid in 2 patients; the culture of a sample obtained from 1 patient grew *Staphylococcus epidermidis*, and the other patient had two episodes of *Propionibacterium acnes* infection. These device-related infections were diagnosed by culture and occurred without reports of headache, fever, photophobia, or nuchal rigidity. The 2 patients were treated with antibiotics and removal of the intraventricular device, which led to an interruption in treatment. The patients continued treatment after device replacement. One patient had grade 3 device leakage owing to the rupture of the silicone dome of the intraventricular device, and 1 patient had

Table 2. Adverse Events (Safety Population).*

Adverse Event	Patients (N=24)
	no. (%)
Common adverse events	
Convulsions†	23 (96)
Pyrexia	17 (71)
Vomiting	15 (63)
Hypersensitivity events‡	15 (63)
Upper respiratory tract infection	13 (54)
Nasopharyngitis	10 (42)
Rhinitis	10 (42)
Serious adverse events	
Any	20 (83)
Hypersensitivity	7 (29)
Upper respiratory tract infection§	5 (21)
Epilepsy¶	4 (17)
Pharyngitis‖	4 (17)
Gastroenteritis	3 (13)
Pyrexia	2 (8)
Device-related infection**	2 (8)

* Common adverse events were those reported in more than 35% of the patients. Serious adverse events were those reported in more than 1 patient. A complete list of serious adverse events is provided in Table S5 in the Supplementary Appendix.

† The category of convulsions includes seizure (in 14 patients [58%]); epilepsy and generalized tonic–clonic seizure (in 12 [50%] each); petit mal epilepsy (in 7 [29%]); atonic seizures, drop attacks, partial seizures, or seizure cluster (in 2 [8%] each); and clonic convulsion, complex partial seizures, myoclonic epilepsy, status epilepticus, or tonic convulsion (in 1 [4%] each).

‡ Hypersensitivity events include hypersensitivity (in 9 patients [38%]); conjunctivitis (in 4 [17%]); contact dermatitis, rash, or urticaria (in 2 [8%] each); and atopic dermatitis, dermatitis, or seasonal allergy stomatitis (in 1 [4%] each).

§ This category includes upper respiratory infection (in 4 patients [17%]) and adenoviral upper respiratory infection (in 1 [4%]).

¶ This category includes epilepsy (in 2 patients [8%]) and generalized tonic–clonic seizure or seizure (in 1 [4%] each).

‖ This category includes bacterial pharyngitis (in 2 patients [8%]) and pharyngitis or viral pharyngitis (in 1 [4%] each).

** This category includes *Staphylococcus epidermidis* or *Propionibacterium acnes* device-related infection. A complete list of device-related adverse events is provided in Table S7 in the Supplementary Appendix.

a grade 3 increase in the white-cell count in the cerebrospinal fluid. Other device-related adverse events, including needle displacement and device leakage, were grade 1 in severity.

The cerebrospinal fluid was tested before each infusion. An increased white-cell count was seen throughout the study in 4 patients (17%) who were asymptomatic without evidence of infection on Gram's staining and culture. Changes that were seen on 12-lead electrocardiography (nonspecific repolarization abnormalities, sinus arrhythmia, superventricular extrasystoles, and biphasic T waves) in 17 patients (71%) were determined not to be clinically adverse by the investigators. Transient asymptomatic decreases in blood pressure that occurred in more than 2 consecutive measurements were observed in 8 patients (33%).

DISCUSSION

In a small group of children with CLN2 disease who were between the ages of 3 and 16 years, the rate of clinical decline was lower among those who received intraventricular infusion of cerliponase alfa than among historical controls. The study was designed as an open-label, single-group study and an extension study. A statistical comparison with a historical control group (including patient-level matching and covariate adjustments) was used to control for possible confounders. A treatment benefit was shown in the efficacy population over a period of at least 96 weeks, although the treatment period was longer for most patients at the time of the data cutoff (median, 116 weeks; range, 96 to 145). All 23 patients in the efficacy population continued in the extension study. Among the treated patients, the annual rate of loss of total gray-matter volume during a 96-week period was 6.7%, with larger decreases seen during the first year of treatment than during the second year.

Intraventricular administration maximizes delivery of cerliponase alfa to the central nervous system and may reduce the risk of immune-mediated adverse events that have been associated with systemic enzyme-replacement therapy.[15-17] Serious adverse events reflected treatment with exogenous protein into the ventricular system and complications from the intraventricular device. Three serious device-related infections occurred in two patients. Both patients continued therapy after removal of the intraventricular device, treatment with antibiotics, and subsequent replacement of the device, but treatment with cerliponase alfa was delayed. Serious adverse events also included device leakage and hypersensitivity reactions. Further study is required to determine whether intraventricular enzyme-replacement treatment is appropriate in other lysosomal storage disorders that have manifestations in the central nervous system.

In conclusion, intraventricular administration of cerliponase alfa every 2 weeks at a dose of 300 mg in children with CLN2 disease resulted in a slower rate of decline in motor and language function than that in historical controls. The potential uses of intraventricular cerliponase alfa to prevent the onset of symptoms in young patients and to delay or prevent changes in vision warrant further study. Intraventricular enzyme-replacement therapy was associated with device-related complications, including grade 3 infection, leakage, and an increased white-cell count in cerebrospinal fluid in half the patients.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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