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Cerliponase alfa for the treatment of CLN2 disease in a patient cohort including children under 3 years of age

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Background

- Cerliponase alfa is a recombinant human tripeptidyl peptidase 1 (TPP1) enzyme replacement therapy for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2 disease) caused by mutations in the TPP1 gene[1]
- Open-label studies in children over 3 years of age with CLN2 disease showed that biweekly intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa slowed deterioration in motor and language function[2,3]
- We report findings from a completed study to assess safety and efficacy of cerliponase alfa in an expanded cohort including children <3 years (NCT02678689)

Methods

Study Design

- Open-label, multicenter, international trial of cerliponase alfa for approximately 3 years (144 weeks)
- Cerliponase alfa dose was age-adjusted for children <2 years

Objectives

- Primary objectives:
  - Evaluate safety and tolerability of ICV cerliponase alfa
  - Evaluate treatment effectiveness as a delay in progression of motor-language score on the CLN2 Clinical Rating Scale
- Secondary objectives: assess immunogenicity of cerliponase alfa in CSF and serum; characterize the pharmacokinetics of cerliponase alfa in CSF and plasma; measure MRI parameters of disease progression; assess impact of treatment on the total CLN2 Clinical Rating Scale; assess the time to disease manifestation for asymptomatic patients

Key Eligibility Criteria

- ***Inclusion***: diagnosis of CLN2 disease as determined by TPP1 enzyme activity; motor-language score 3–6 at Screening; <18 years of age at the time of informed consent
- ***Exclusion***: other inherited neurologic disease, other neurological illness that may interfere with disease rating; percutaneous feeding tube placement prior to enrollment; presence of ventricular abnormality or ventricular shunt; episode of generalized motor status epilepticus or severe infection in 4 weeks before first dose visit

Efficacy Evaluations

- The primary efficacy endpoint was the rate of decline in motor-language domains of the CLN2 Clinical Rating Scale
  - The CLN2 Clinical Rating Scale comprises 4 domains: motor, language, vision, and seizures; each domain is scored from 0 (complete loss of function) to 3 (normal function)[4]
- Time to 2-point decline or score of 0 in the motor-language score was analyzed using Kaplan Meier methods and the Cox proportional hazards model
- For analyses of motor-language score, treated patients were compared with historical natural history (NH) controls; NH patients were matched (up to 3:1) to treated participants on age (±3 months), genotype (equal number of common alleles c.622C>T, c.509.1G), and baseline motor-language score (exact match)
- Changes in brain volume of treated participants were assessed by cranial MRI

Safety Evaluations

- Safety assessments included: incidence, severity, and relationship to cerliponase alfa of treatment adverse events (AEs); clinical laboratory results (including chemistry, hematology, urinalysis, and cerebrospinal fluid [CSF]); vital signs; physical examinations; ECGs; EEGs; concomitant medications; immunogenicity

Results

Table 1. Subject demographics, baseline characteristics and disposition

		N = 14
Disposition, n (%)	Treated Completed treatment Completed study Discontinued study[a]	14 (100) 13 (93) 13 (93) 1 (7)
Sex, n (%)	Male Female	6 (43) 8 (57)
Race, n (%)	White	14 (100)
Ethnicity, n (%)	Hispanic or Latino Not Hispanic or Latino	2 (14) 12 (86)
Baseline age, years	mean (SD) median (min, max)	3.1 (1.5) 2.7 (1.1, 6.0)
Baseline age category, n (%)	<2 years <3 years ≥3 years	5 (36) 8 (57) 6 (43)
Baseline motor-language score	mean (SD) median (min, max)	4.6 (1.7) 5.5 (1, 6)

[a]One subject discontinued study to receive cerliponase alfa commercially
max, maximum; min, minimum; SD, standard deviation

Table 2. Cerliponase alfa exposure

	Baseline Age			Total (n = 14)
	< 2 years (n = 5)	**< 3 years** (n = 8)	**≥ 3 years** (n = 6)	
Duration of treatment,[a] weeks mean (SD) median min, max	 142.0 (0.3) 142.0 141.6, 142.4	 142.0 (0.4) 141.9 141.6, 142.6	 138.2 (9.1) 141.9 119.7, 142.1	 140.4 (6.0) 141.9 119.7, 142.6

[a]Any dose
max, maximum; min, minimum; SD, standard deviation

Efficacy

Motor-language score outcomes

- 29 NH patients were matched (up to 3:1) with 12 treated participants on baseline age, genotype, and baseline motor-language score; 2 treated patients could not be matched with an NH control
- Rate of decline in motor-language score was significantly lower for treated participants compared with matched untreated NH patients, across all patient ages
- No decline in motor-language score was seen in treated patients < 2 years of age

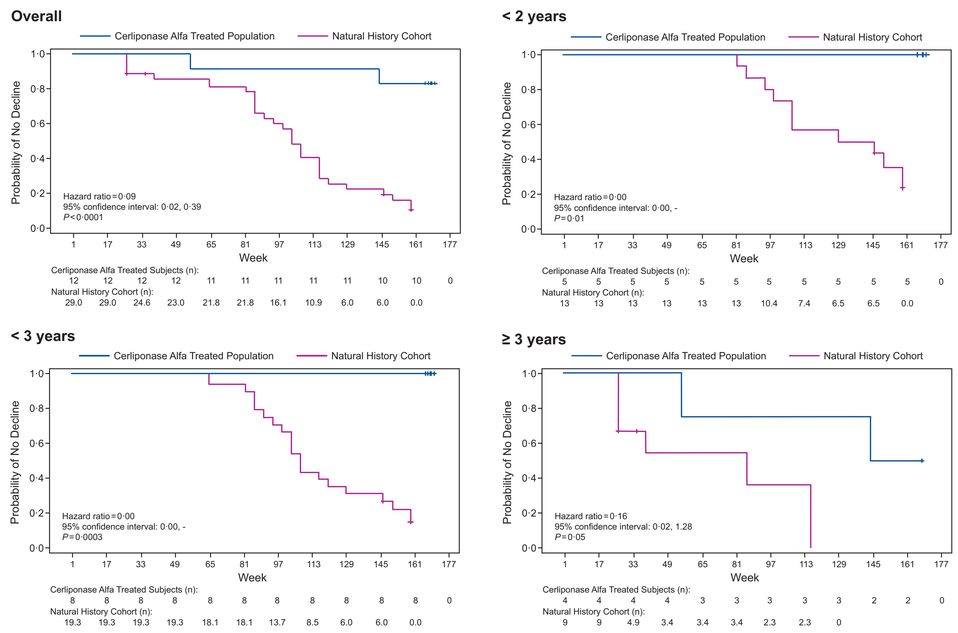
Table 3. Rate of decline in motor-language score

Rate of decline in motor-language score points/48 weeks	NH Controls (n = 29)	190-203 (n = 12)
Overall		
mean (SD) median (min, max)	*n* = 29 1.30 (0.86) 1.28 (0.00, 3.73)	*n* = 12 0.15 (0.24) 0.00 (0.00, 0.66)
	mean difference: 1.15 (95% CI: 0.80, 1.50); *P* < 0.0001	
< 2 years at baseline		
mean (SD) median (min, max)	*n* = 13 0.88 (0.57) 0.83 (0.00, 2.24)	*n* = 5 0.00 (0.00) 0.00 (0.00, 0.00)
	mean difference: **0.88** (95% CI: 0.52, 1.24); *P* = 0.0002	
< 3 years at baseline		
mean (SD) median (min, max)	*n* = 20 1.09 (0.56) 1.18 (0.00, 2.24)	*n* = 8 0.04 (0.10) 0.00 (0.00, 0.29)
	mean difference: **1.05** (95% CI: 0.78, 1.33); *P* < 0.0001	
≥ 3 years at baseline		
mean (SD) median (min, max)	*n* = 9 1.72 (1.22) 1.87 (0.00, 3.73)	*n* = 4 0.38 (0.30) 0.43 (0.000, 0.66)
	mean difference: **1.34** (95% CI: 0.41, 2.28); *P* = 0.0097	

CI, confidence interval; max, maximum; min, minimum; NH, natural history; SD, standard deviation

- Compared with matched NH controls, treated participants were significantly less likely to experience an unreversed 2-point decline or score of 0 in motor-language score
  - Treated patients < 3 years of age did not experience an unreversed 2-point decline or score of 0 in motor-language score
- Among the 8 patients who were < 3 years at baseline, 7 patients started with a motor-language score of 6 and all 7 maintained a score of 6 at the end of study
  - All 7 patients with motor-language score of 6 at study end also had a total CLN2 Clinical Rating Scale score of 12

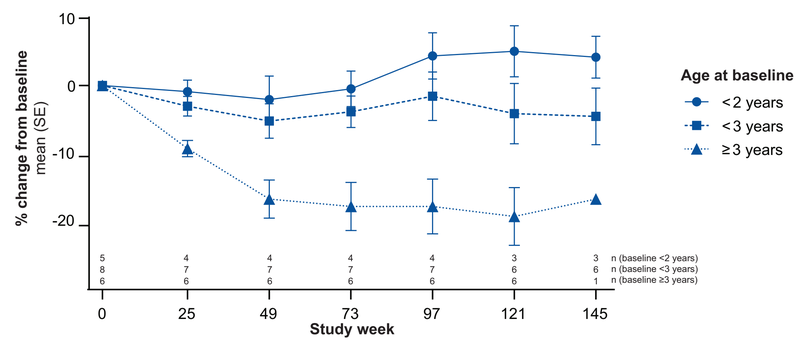
Figure 1. Time to unreversed 2-point decline or score 0 in motor-language score



MRI assessments of gray matter volume

- Treated participants age ≥ 3 years at baseline showed decreases in mean total gray matter volume that stabilized after week 49: mean percent change from baseline was -16.9 % at week 49 and -16.9% at week 145
- Total gray matter volume was stable in treated participants who were < 2 years of age at baseline: mean percent change from baseline at weeks 49 and 145 was -2.1% and +4.2%, respectively

Figure 2. Change in gray matter volume



Safety

- All participants experienced at least 1 AE; most were mild or moderate in severity (Grade 1 or 2); 10 patients experienced Grade 3 AEs; one participant had a Grade 4 AE of gastrointestinal fistula not related to study drug
- 53 study drug-related AEs were reported in 11 participants (78.6%); the most common drug-related AE were pyrexia, hypersensitivity, and body temperature increased
  - The incidence and severity of hypersensitivity events was higher in the group who were age < 3 years at baseline compared with those age ≥ 3 years at baseline
- A total of 41 serious AEs (SAEs) were reported in 12 participants; 10 SAEs in 7 participants were considered related to study drug, including 7 events of pyrexia (4 participants), 2 events of hypersensitivity (2 participants), and 1 event of anaphylactic reaction
- There were no deaths and no AEs resulting in permanent discontinuation of study drug or discontinuation from the study
- A total of 74 AEs mapping to the Convulsions Standardized MedDRA Query were experienced by 8 participants; 64 (87%) convulsion AEs occurred in 5 out of 7 participants with motor-language score < 6 at baseline; 10 (14%) occurred in 3 out of 7 participants with motor-language score of 6 at baseline

Table 4. Adverse event summary

n (%)	Baseline Age			Total (n = 14)
	< 2 years (n = 5)	**< 3 years** (n = 8)	**≥ 3 years** (n = 6)	
Any AE Grade 1 Grade 2 Grade 3 Grade 4	5 (100) 5 (100) 5 (100) 4 (80) 0	8 (100) 8 (100) 8 (100) 5 (63) 0	6 (100) 6 (100) 6 (100) 5 (83) 1 (17)	14 (100) 14 (100) 14 (100) 10 (71) 1 (7)
AE leading to dose reduction	0	0	0	0
AE leading to dose interruption	3 (60)	4 (50)	1 (17)	5 (36)
AE leading to study drug discontinuation	0	0	0	0
Any SAE	3 (60)	6 (75)	6 (100)	12 (86)
Death	0	0	0	0
Any drug-related AE Pyrexia Hypersensitivity Body temp increased Anaphylactic reaction Asthenia ECG abnormal Headache	5 (100) 3 (60) 3 (60) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20)	8 (100) 5 (63) 4 (50) 1 (13) 1 (13) 1 (13) 1 (13) 1 (13)	3 (50) 3 (50) 0 0 0 0 0 0	11 (79) 8 (57) 4 (29) 1 (7) 1 (7) 1 (7) 1 (7) 1 (7)

AE, adverse event; SAE, serious adverse event

Conclusions

- ICV-administered cerliponase alfa slowed the decline in motor and language function in children with CLN2 disease, including those < 3 years of age, with a safety profile consistent with prior studies
  - Outcomes in patients who initiated treatment at ≥ 3 years were consistent with findings from the 190-201/202 studies
- Additionally, these results may suggest that early initiation of treatment can delay symptom onset

References

1. Aylward et al. *Exp Opin Orphan Drugs* 2020;8(11):445-454. **2.** Schulz et al. *N Engl J Med* 2018;378:1898-1907. **3.** Schulz et al. *Lancet Neurol* 2024; 23:60-70. **4.** Wyrwich KW et al. *J Inborn Errors Metab Screening* 2018;6:1-7.

Disclosures

This study was funded by BioMarin Pharmaceutical Inc.

Presented at the 20th Annual WORLD *Symposium*: Feb 4-9, 2024; San Diego, CA, USA