Cerliponase alfa for the treatment of CLN2 disease: Combined results from two ongoing observational studies

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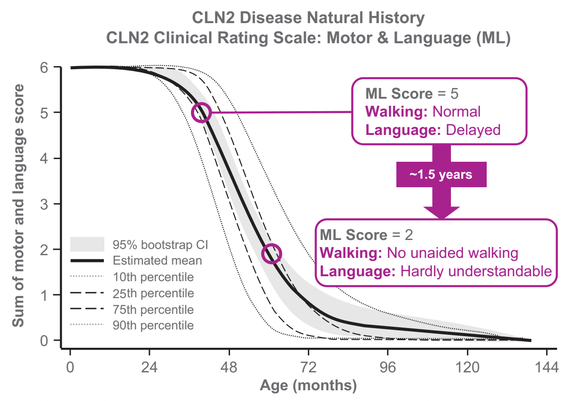
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Introduction

CLN2 disease is a rare and rapidly progressing pediatric neurodegenerative lysosomal disorder

- CLN2 disease is caused by autosomal recessive inheritance of pathogenic *TPP1* gene variants, which lead to deficient activity of the TPP1 enzyme
- Resulting accumulation of lysosomal storage materials induces cell death and neurodegeneration leading to progressive disease manifestation:
  - Motor function decline
  - Language delay
  - Seizures/epilepsy
  - Dementia
  - Vision loss
  - Death by mid adolescence



CLN2 Clinical Rating Scale figure adapted from Nickel M, et al. *Lancet Child Adolesc Health* 2018;2:582–90CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor-language; TPP1, tripeptidyl peptidase 1.

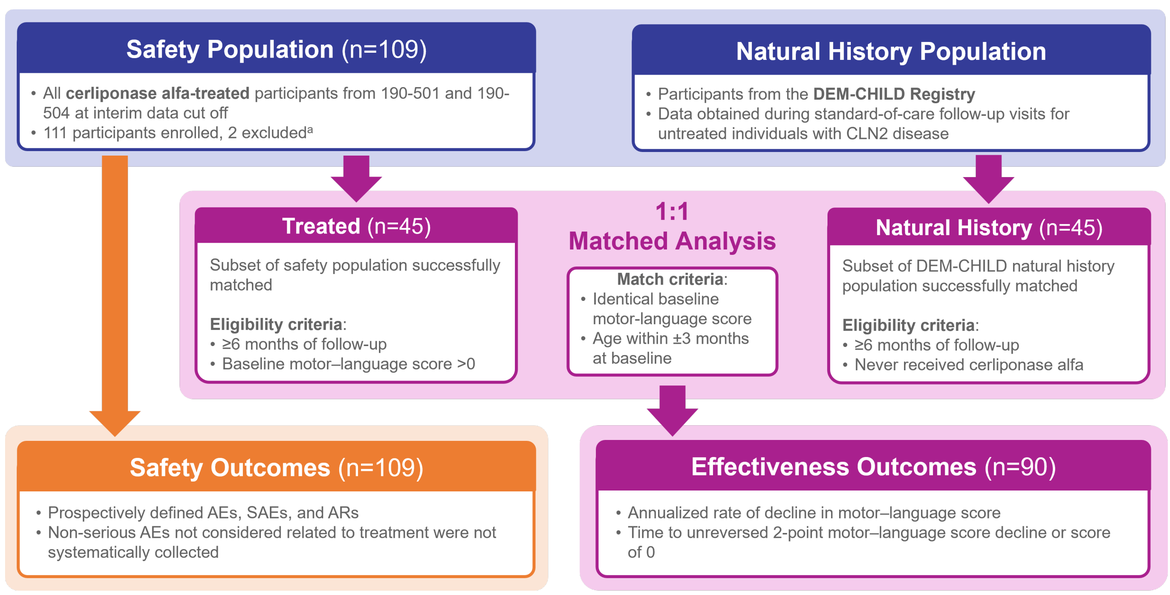
- Intracerebroventricular enzyme replacement therapy with cerliponase alfa (recombinant human TPP1) is currently the only approved disease-modifying therapy for CLN2 disease
- The efficacy and safety of cerliponase alfa has been demonstrated in children with CLN2 disease (aged 3–16 years) in the pivotal 48-week, multicenter, study (NCT01907087), an open-label extension study (NCT02485899) with up to 240 weeks of follow-up, and in a study (NCT02678689) which assessed safety and efficacy in a cohort that included children under 3 years of age
  - Intracerebroventricular administration of cerliponase alfa was shown to slow decline in motor and language function compared with natural history controls, and was generally well tolerated
- Two observational, post-marketing surveillance studies assessing long-term, real-world outcomes with cerliponase alfa are currently ongoing in the USA (study 190-501, NCT04476862) and EU (study 190-504, EUPAS29031); combined interim results from these studies are presented here

Methods

Cerliponase alfa real-world observational program

- The 190-501 and 190-504 studies are ongoing, multicenter, observational studies of cerliponase alfa for the treatment of CLN2 disease
  - The 190-501 study enrolled participants at 16 sites in the United States, and was initiated in August 2020, with an interim data cut-off in March 2025
  - The 190-504 study enrolled participants at 12 sites across Europe, and was initiated in October 2019, with an interim data cut-off of May 2025
- Pooled interim data from these studies were analyzed to assess safety outcomes during longer-term treatment with cerliponase alfa and evaluate treatment effectiveness relative to matched natural history controls from the DEM-CHILD database

Pooled interim analysis



The cut-off dates for 190-501 and 190-504 were 18th March 2025 and 8th May 2025, respectively
[a]Two participants were excluded from safety analyses because data were not available beyond consent.
AE, adverse event; AR, adverse reaction; CLN2, neuronal ceroid lipofuscinosis type 2; SAE, serious adverse event

Results

Demographics and clinical characteristics

Baseline characteristic	Enrolled population (N=111)	Matched analysis: Treated (n=45)	Matched analysis: Natural history (n=45)
Female, n (%)	54 (49)	26 (58)	20 (44)
Race, n (%)[a]			
American Indian or Alaska Native	3 (3)	2 (4)	0
Asian	4 (4)	1 (2)	0
Black or African American	1 (1)	0	0
White	82 (74)	37 (82)	0
Multiple	2 (2)	0	0
Not reported	17 (15)	5 (11)	45 (100)
Age (years), mean (SD)			
At diagnosis	4.0 (2.4)	3.8 (1.2)	4.9 (1.3)
At baseline[b]	4.6 (2.5)	4.3 (0.9)	4.3 (0.9)
Baseline motor–language score, mean (SD)	4.1 (1.3)	3.8 (1.1)	3.8 (1.1)
Genotype, n (%)[c]			
2 common alleles	23 (21)	11 (24)	26 (58)
1 common allele	36 (32)	14 (31)	12 (27)
0 common alleles	37 (33)	13 (29)	7 (16)
Not available	15 (14)	7 (16)	0

[a]Data for 17 participants (15%) were not provided due to participant privacy rules
[b]Baseline is defined as the last assessment prior to first treatment with cerliponase alfa in treated participants and as the timepoint at which the natural history participant was matched with the treated participant in the natural history cohort
[c]Common alleles were defined as c.622C>T and c.509-1G>C
CLN2, neuronal ceroid lipofuscinosis type 2; SD, standard deviation.

Safety

- Safety analyses included 109 treated individuals with a mean (SD) cerliponase alfa exposure time of 5.6 (2.5) years
  - 67 participants (61.5%) experienced adverse events (AEs), 49 participants (45.0%) experienced Grade ≥3 AEs; serious AEs were reported in 56 participants (51.4%) and device-related AEs in 37 participants (33.9%)

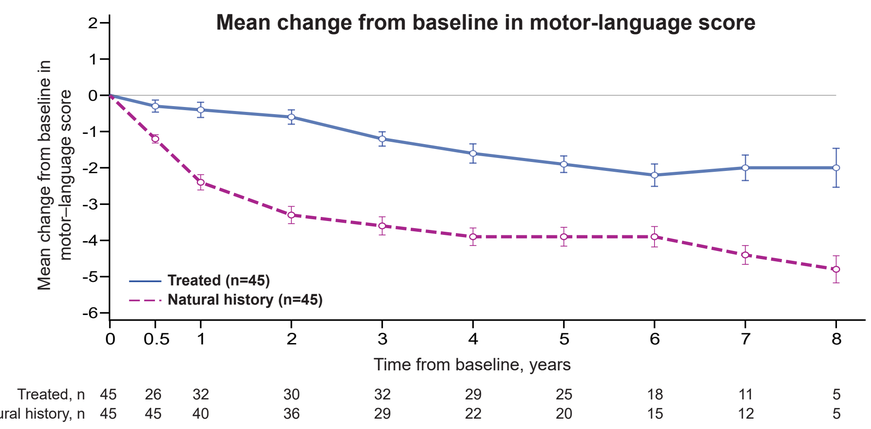
Overall summary of AEs, n (%)	Total (N=109)[a]
Any AE	67 (61.5)
Any SAE	56 (51.4)
Most common SAEs	
Seizure	15 (13.8)
Device-related infections	8 (7.3)
Device end of service	7 (6.4)
Device malfunction	7 (6.4)
Treatment related SAE	6 (5.5)
Any AE of Grade ≥3[b]	49 (45.0)
Deaths	6 (5.5)

Participants with any AEs of interest, n (%)[c]	Total (N=109)[a]
Temporally-related adverse reactions[d]	42 (38.5)
Device-related events	37 (33.9)
Convulsions	21 (19.3)
Hypersensitivity reactions	9 (8.3)
Meningitis	5 (4.6)
Cardiovascular events	3 (2.8)
Anaphylactic reactions	0
Hydrocephalus	0

[a]Two participants were excluded from safety analyses with no data available. [b]Defined by common terminology criteria for adverse events. [c]Prospectively selected based on non-clinical findings, known treatment class effects, and literature review of AEs. [d]Occurring within 24 hours following treatment.

Motor-language score: change from baseline

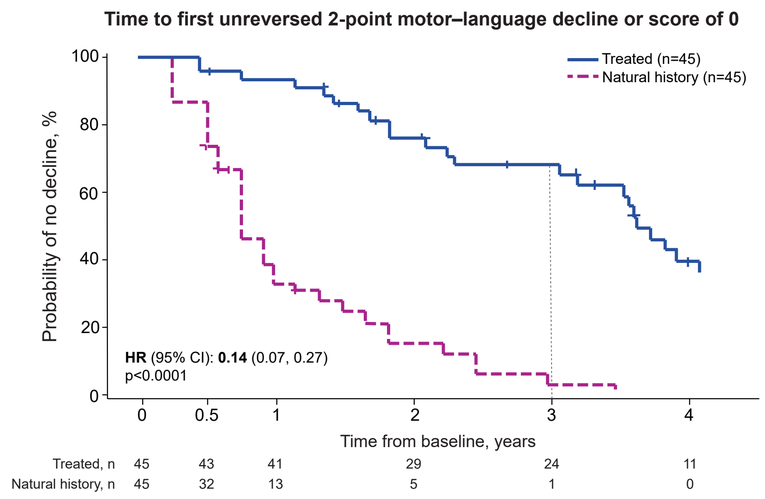
- Cerliponase alfa-treated participants experienced a slower rate of decline in motor and language function compared with matched natural history controls

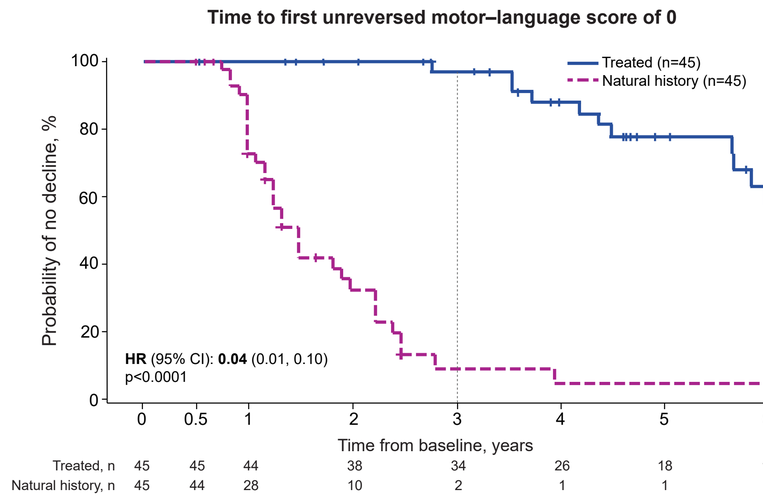


Mean (SD) duration of follow-up was 8.3 (4.8) in both groups. Matching is 1:1 based on age and baseline motor–language score
CI, confidence interval; HR, hazard ratio; SD, standard deviation

Motor-language score: time to unreversed 2-point decline or score of 0

- Cerliponase alfa-treated participants were significantly less likely to experience a decline in motor–language score than matched natural history controls





Mean (SD) treatment exposure was 5.3 (2.3) years.
CI, confidence interval; HR, hazard ratio

Conclusions

- In real-world use, long-term cerliponase alfa slowed motor-language decline in children with CLN2 disease, with no new safety signals
- These results confirm the sustained benefit seen in clinical trials, now across a broader real-world population
- Longer follow-up from these ongoing studies will further define long-term outcomes

References

1. Sleat DE et al. *Am J Hum Genet* 1999;64:1511–23. **2.** Schulz A et al. *Biochim Biophys Acta* 2013;1832:1801–6. **3.** Nickel M et al. *Lancet Child Adolesc Health* 2018;2:582–90. **4.** Mole SE, Williams RE. Neuronal ceroidlipofuscinoses. 2001 Oct 10 [Updated 2013 Aug 1]. **5.** Schulz A et al. *N Engl J Med* 2018;378:1898–907. **6.** Schulz A et al. *Lancet Neurol* 2024;23:60–70. **7.** Schulz A et al. Oral presentation at the 18th International Congress on Neuronal Ceroid Lipofuscinoses. September 26–30, 2023; Hamburg, Germany. **8.** Schulz A et al. Poster at WORLDSymposium, San Diego, CA, February 4–9, 2024.

Acknowledgments

We thank the study sites, participants, and their families for contributing important data supporting this study.

Disclosures

This poster was previously presented at Society for the Study of Inborn Errors of Metabolism (SSIEM), 2026

The 190-501 and 190-504 studies are funded by BioMarin Pharmaceutical Inc.

Emily de los Reyes has received consulting fees from Neela Therapeutics.
She received travel support from and was an Investigator in BMN 190 clinical trials for BioMarin Pharmaceutical Inc.

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