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# 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

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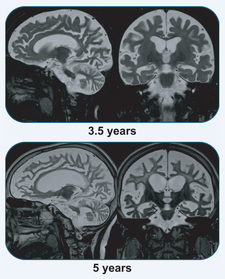
## Introduction

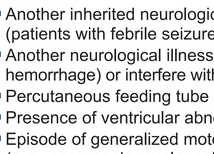
### CLN2 Disease: A Form of Batten Disease




- Autosomal recessive form of neuronal ceroid lipofuscinosis (NCL)
  - The most common group of neurodegenerative disorders in children and adolescents
  - Share core set of symptoms: seizures, progressive cognitive and motor deterioration, blindness, and premature death
- Deficiency in TPP1 enzyme leads to accumulation of lysosomal storage material, cell dysfunction, and death
- Symptom onset typically at 2–4 years presenting with unprovoked seizures and language delay
- Rapid progressive neurodegeneration leads to early death

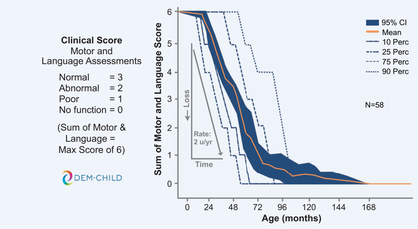
### Cerliponase Alfa: Approved Therapy for CLN2 Disease

- Cerliponase alfa is a recombinant human form of tripeptidyl peptidase 1 enzyme (rhTPP1)[1] approved for treatment in the US and EU in 2017, and subsequently in a number of other countries worldwide




- Administered through an implanted Rickham or Ommaya device into the lateral cerebral ventricle
- 300 mg dose every 14 days via intracerebroventricular (ICV) infusion over ~4 hours
- Age-appropriate doses for children <2 years old (ongoing study 190-203)

### Natural History of CLN2 Disease: Children Decline ~2 Points per Year in Motor-Language Score[2]




- Motor and language loss central to disease morbidity and is primary outcome measure
- Vision loss delayed in comparison to dementia/gait
- Seizure score lacks correlation to disease severity

**Clinical Rating Scale**
(Motor-Language CLN2 Score and Total Score)

| Primary Analysis | | | Supporting Analysis | | |
|---|---|---|---|---|---|
| **Motor** | 3 | Walks normally | **Visual** | 3 | Recognizes and coordinated reach to objects |
| | 2 | Frequent falls, ataxia, independently walk >10 steps | | 2 | Uncoordinated reach to objects |
| | 1 | No unaided gait | | 1 | Reacts to light |
| | 0 | Immobile, mostly bedridden | | 0 | No reaction to visual stimuli |
| **Language** | 3 | Normal | **Seizures** (Grand Mal) | 3 | No seizures in 3 months |
| | 2 | Loss of words, intelligible but abnormal speech | | 2 | 1–2 seizures in 3 months |
| | 1 | Some comprehension, mostly unintelligible speech | | 1 | 1 seizure per month |
| | 0 | Unintelligible or no speech | | 0 | >1 seizure per month |

DEM-CHILD NCL database

## Objectives and Methods

### Study 190-203 Design

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

***Objectives***

- Primary objectives of the study include:
  - Evaluate safety and tolerability of cerliponase alfa administered via intracerebroventricular (ICV) device
  - Evaluate treatment effectiveness as a delay in progression of motor-language (ML) score on the Hamburg CLN2 clinical rating scale
- Secondary objectives of the study include:
  - Measure MRI parameters of disease progression
  - Assess impact of treatment on the total Hamburg clinical rating scale
  - Assess the time to disease manifestation for asymptomatic patients

### Key Eligibility Criteria

***Inclusion***

- Diagnosis of CLN2 disease as determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at Screening.
- Quantitative clinical assessment of the Hamburg ML aggregate score 3-6 at Screening, as defined in the Ratings Assessment Guideline
- <18 years of age at the time of informed consent

***Exclusion***

- Another inherited neurologic disease, e.g., other forms of NCL or seizures unrelated to CLN2 disease (patients with febrile seizures may be eligible)
- Another neurological illness that may have caused cognitive decline (e.g., trauma, meningitis, hemorrhage) or interfere with disease rating (autism) before Screening
- Percutaneous feeding tube placement prior to enrollment
- Presence of ventricular abnormality (hydrocephalus, malformation) or presence of ventricular shunt
- Episode of generalized motor status epilepticus or severe infection (e.g., pneumonia, pyelonephritis, or meningitis) within 4 weeks before the first dose visit

### Efficacy Evaluation

- The primary efficacy endpoint is the rate of decline in the 0 to 6-point ML score
- Natural history subjects were matched (up to 3:1) to treated subjects, on the basis of age (within 3 months), genotype (equal number of common alleles c.622C>T, c.509.1G), and baseline ML score (exact match)

## Results

### Subject Demographics, Baseline Characteristics, and Disposition

| | | 190-203 |
|---|---|---|
| **Disposition,** n (%) | Enrolled | 14 (100.0%) |
| | Treated | 14 (100.0%) |
| | Completed study | 10 (71.4%) |
| | Continuing on treatment | 3 (21.4%) |
| | Discontinued from study | 1 (7.1%)[a] |
| **Age at enrollment,** years | mean (SD), median | 3.0 (1.46), 2.6 |
| **Age category,** n (%) | <3 years | 8 (57.1%) |
| | <2 years | 5 (35.7%) |
| **Sex,** n (%) | Female | 8 (57.1%) |
| | Male | 6 (42.9%) |
| **Baseline ML score,** n (%) | 6 | 7 (50.0%) |
| | 5 | 1 (7.1%) |
| | 4 | 3 (21.4%) |
| | 3 | 1 (7.1%) |
| | 2 | 1 (7.1%) |
| | 1 | 1 (7.1%) |
| | mean (SD), median | 4.6 (1.69), 5.5 |

[a]One subject discontinued from the study because they were able to receive cerliponase alfa commercially at home

### Study Drug Exposure

| **Study Drug Exposure,** weeks | N=14 |
|---|---|
| mean (SD) | 127.0 (26.94) |
| median [min, max] | 141.9 [64.4, 142.6] |

### Adverse Event Summary

| Summary of AEs[a] | Baseline Age (years) | | | Overall |
|---|---|---|---|---|
| | < 2 (N=5) | < 3 (N=8) | ≥3 (N=6) | (N=14) |
| Any AE, n (%) | 5 (100.0%) | 8 (100.0%) | 6 (100.0%) | 14 (100.0%) |
| Any AE Grade 1 | 5 (100.0%) | 8 (100.0%) | 6 (100.0%) | 14 (100.0%) |
| Any AE Grade 2 | 5 (100.0%) | 8 (100.0%) | 6 (100.0%) | 14 (100.0%) |
| Any AE Grade 3 | 3 (60.0%) | 4 (50.0%) | 5 (83.3%) | 9 (64.3%) |
| Any AE Grade 4 | 0 | 0 | 1 (16.7%) | 1 (7.1%) |
| AE Drug-Related, n (%) | 5 (100.0%) | 8 (100.0%) | 3 (50.0%) | 11 (78.6%) |
| AE Drug-related Grade 1 | 4 (80.0%) | 5 (62.5%) | 2 (33.3%) | 7 (50.0%) |
| AE Drug-related Grade 2 | 2 (40.0%) | 5 (50.0%) | 3 (50.0%) | 7 (50.0%) |
| AE Drug-related Grade 3 | 3 (60.0%) | 3 (37.5%) | 0 | 3 (21.4%) |
| AE Drug-related Grade 4 | 0 | 0 | 0 | 0 |
| Any SAE, n (%) | 3 (60.0%) | 6 (75.0%) | 6 (100.0%) | 12 (85.7%) |

| Common AEs[b] | Overall (N=14) |
|---|---|
| Pyrexia | 12 (85.7%) |
| Upper respiratory tract infection | 12 (85.7%) |
| Gastroenteritis | 7 (50.0%) |
| Extensor plantar response | 6 (42.9%) |
| Generalized tonic-clonic seizure | 6 (42.9%) |
| Hypersensitivity | 5 (35.7%) |
| Speech disorder developmental | 5 (35.7%) |
| Vomiting | 5 (35.7%) |

[a]Subjects who experienced >1 AE with a given Grade or PT were counted once in the highest grade of the AE
[b]Most common AEs seen in >35% subjects

- All patients experienced at least 1 AE; the most common treatment-emergent AEs were pyrexia (85.7%), upper respiratory tract infection (85.7%), gastroenteritis (50.0%), extensor plantar response (42.9%) and generalized tonic-clonic seizure (42.9%)
- Most AEs were mild or moderate in severity (Grade 1 or 2); 9 subjects experienced Grade 3 AEs; one subject had a Grade 4 AE of gastrointestinal fistula not related to study drug
- There were no deaths and no AEs resulting in permanent discontinuation of study drug or discontinuation from the study; there were no notable differences in the incidence of AEs between age subgroups or relative to the overall safety population

### Serious Adverse Event Summary

| SAEs | Overall (N=14) | SAEs | Overall (N=14) |
|---|---|---|---|
| Pyrexia | 4 (28.6%) | Hypoxia | 1 (7.1%) |
| Hypersensitivity | 2 (14.3%) | Infection | 1 (7.1%) |
| Influenza | 2 (14.3%) | Medical device hematoma | 1 (7.1%) |
| Adenoidal hypertrophy | 1 (7.1%) | Medical device site irritation | 1 (7.1%) |
| Anaphylactic reaction | 1 (7.1%) | Mycoplasma infection | 1 (7.1%) |
| Cerebral disorder | 1 (7.1%) | Periorbital hematoma | 1 (7.1%) |
| Complications of device insertion | 1 (7.1%) | Pneumonia | 1 (7.1%) |
| Coronovirus infection | 1 (7.1%) | Priopionobacterium test positive | 1 (7.1%) |
| CSF cell count increased | 1 (7.1%) | Pyelonephritis | 1 (7.1%) |
| Dental caries | 1 (7.1%) | Rhinitis | 1 (7.1%) |
| Device leakage | 1 (7.1%) | Rhinovirus infection | 1 (7.1%) |
| Dysphagia | 1 (7.1%) | Status epilepticus | 1 (7.1%) |
| Esherichia urinary tract infection | 1 (7.1%) | Upper respiratory tract infection | 1 (7.1%) |
| Gastrointestinal fistula | 1 (7.1%) | Viral infection | 1 (7.1%) |

- A total of 40 SAEs were reported in 12 subjects: SAEs reported more than once included pyrexia (7 SAEs in 4 subjects), influenza (3 SAEs in 2 subjects), pneumonia (3 SAEs in 1 subject), hypersensitivity (2 SAEs in 2 subjects), and dental caries (2 SAEs in 1 subject)
- Ten SAEs in 7 subjects were considered related to study drug: 7 events of pyrexia (4 subjects), 2 events of hypersensitivity (2 subjects), 1 event of anaphylactic reaction (1 subject)

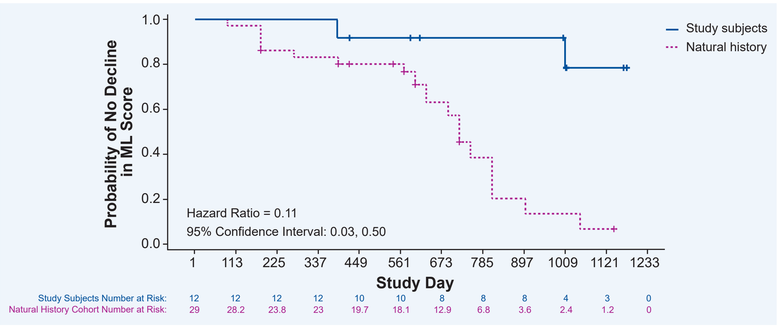
### Rate of Decline in Motor-Language Score

- Twelve of 14 subjects met criteria for matching with evaluable natural history patients
- At Baseline, mean (SD) ML score was 5.0 (1.41) points in the matched 190-203 subjects and 5.0 (1.38) points in the matched natural history comparator cohort
- There was little decline in the observed ML score in 190-203 subjects and a greater than 1-point difference in rate of decline relative to matched natural history comparators

| Rate of Decline in ML Score (points per 48 weeks) | Natural History (N=29) | 190-203 (N=12) | Difference |
|---|---|---|---|
| Mean (SD) | 1.24 (1.022) | 0.14 (0.262) | 1.10 |
| SE | | | (0.204) |
| Median (IQR) | 1.18 (0.45, 1.77) | 0.00 (0.00, 0.17) | |
| 95% CI | 0.85, 1.63 | -0.03, 0.30 | 0.69, 1.52 |

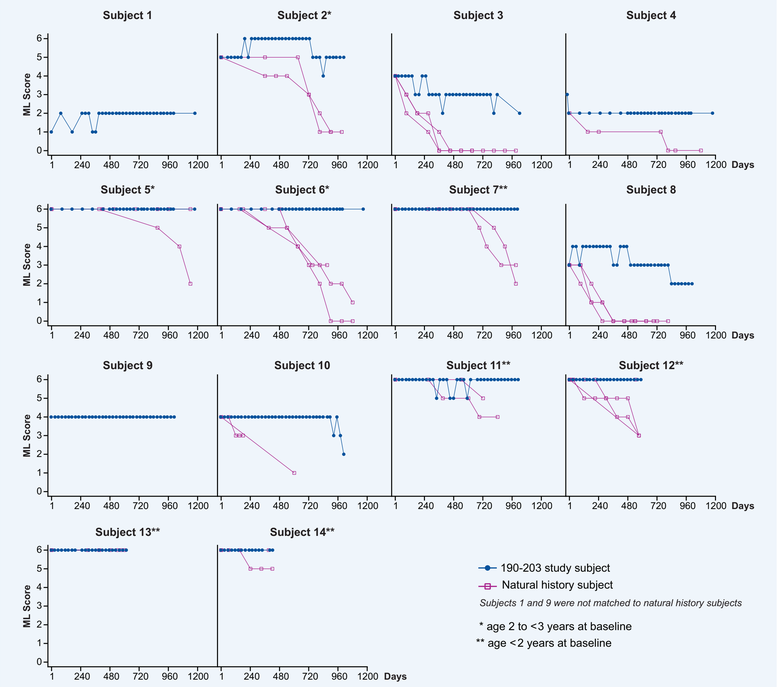
### Time to 2-Point Decline in Motor-Language Score

- A Cox proportional hazards model of time to unreversed 2-point decline or score of 0 in ML score demonstrated an 8- to 9- fold reduction in the likelihood of ML decline in comparison with matched natural history patients (hazard ratio, 0.114; 95% CI, 0.026 to 0.499)




### Motor-Language Score Change from Baseline

- Ten of 14 study 190-203 subjects (71.4%) showed no clinical progression on the ML scale from baseline to last assessment; 1 subject (7.1%) gained a single point; 1 subject (7.1%) lost a single point; 2 subjects (14.3%) lost 2 points
- From the 12 subjects from study 190-203 who were matched to natural history subjects, 11 study 190-203 subjects maintained a higher ML score than the matched natural history subjects; one 190-203 subject with baseline ML score of 6 showed an equivalent trend to their natural history match




## Summary and Conclusions

- Interim results show that ICV-administered cerliponase alfa is generally well-tolerated and has an acceptable safety profile in this population, including subjects <3 years of age
  - As of the data cutoff (26 April 2020), 14 subjects had been enrolled and dosed with cerliponase alfa for 64-143 weeks (mean, 127 weeks)
  - The cohort includes 8 children under 3 years of age and 5 under 2 years of age
  - A new event of anaphylactic reaction was identified during this clinical trial: the information about anaphylactic reaction was included in all Reference Safety Information documents
- Interim analyses suggest an efficacy profile comparable to that observed in prior studies

**References**
**1.** Schulz et al. Study of intraventricular cerliponase alfa for CLN2 disease. *N Engl J Med* 2018;378:1898-1907. **2.** Nickel 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;2:582-590.

**Acknowledgments**
The authors thank the healthcare providers and the patients and their families who participated in this study.

**Disclaimer**
In the US, cerliponase alfa is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.