LB-63

Long-Term Treatment with Intracerebroventricular Cerliponase Alfa for Children with CLN2 Disease: Safety and Efficacy after >5 Years

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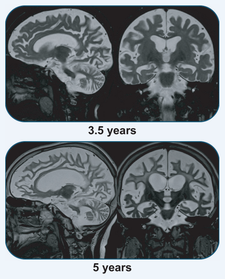
Introduction

CLN2 Disease: A Form of Batten Disease

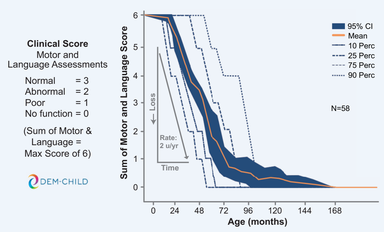


- Autosomal recessive form of neuronal ceroid lipofuscinosis (NCL)
  - The most common group of neurodegenerative disorders in children and adolescents
  - Share core set of symptoms: seizures, progressive cognitive and motor deterioration, blindness, and premature death
- Deficiency in TPP1 enzyme leads 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

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 Design

- **190-201**: 48-week open-label primary study
  - Single arm, multicenter, dose escalation study
  - Dose escalation phase followed by 48-week stable dose phase (300 mg ICV cerliponase alfa every 14 days)
- **190-202:** 240-week open-label extension study
  - 300 mg ICV cerliponase alfa every 14 days for 240 weeks
  - 6-month safety follow up period after completion of 240-week treatment period

Combined data from both the primary and extension studies are shown

Key Eligibility Criteria

- For enrollment in 190-201:
  - Confirmed diagnosis of CLN2 disease by TPP1 enzyme activity and genotype analysis
  - Age 3-15 years at study enrollment
  - No prior stem cell therapy, gene therapy, or enzyme replacement therapy for CLN2 disease
  - Combined motor-language domain score of 3-6 at screening
- For enrollment in 190-202:
  - Completion of 48 weeks treatment at 300 mg dose in study 190-201
  - No loss of 3 or more points on the combined motor-language domains between baseline and 190-201 study completion
  - No score of 0 points on the combined motor-language domains in study 190-201

Key Efficacy Evaluations

- All subjects who received >1 dose of cerliponase alfa (N=23) were included in efficacy analyses and were compared with untreated natural history controls enrolled in the DEM-CHILD NCL registry; efficacy was evaluated from first dose of 300 mg in study 190-201

Primary Efficacy Endpoint

- Time to unreversed 2-point decline or score of 0 in the combined ML score
  - Analyzed by Kaplan-Meier methods and Cox proportional-hazards model; Cox model included baseline combined motor-language score, age, genotype and sex as covariates

Secondary Efficacy Endpoint

- Changes in brain volume assessed by cranial MRI

Exploratory Efficacy Endpoint

- Time of death
  - Analyzed by Kaplan-Meier methods and Cox proportional-hazards model. Survival was measured from birth to time of death (event) or time of last CLN2 assessment (censoring); Cox model included genotype and sex as covariates

Safety Evaluations

- Safety was assessed in all subjects who had an ICV access device implanted (N=24)
- Safety evaluations performed included AEs, clinical laboratory results, vital signs, physical and neurological examinations, ECGs, concomitant medications, and immunogenicity

Results

Subject Disposition, Demographics, and Baseline Characteristics

	Overall (N = 24)
Disposition, n	
Subjects enrolled in primary study (190-201)	24
Subjects who completed primary study and enrolled in extension (190-202)	23*
Subjects who completed planned follow-up in extension (190-202)	17†
Sex, n (%)	
Male	9 (38)
Female	15 (62)
Age, years	
Mean (SD)	4.9 (1.28)
Median (range)	4.6 (3.1, 8.9)
Baseline CLN2 motor-language score (prior to first 300 mg dose in 190-201)	
Mean (SD), median	3.5 (1.2), 3.0
Score, n (%)	
6	2 (8.3)
5	2 (8.3)
4	6 (25.0)
3	11 (45.8)
2	2 (8.3)
1	1 (4.2)
Genotype, n (%)	
≥1 common alleles‡	17 (70.8)
No common alleles	7 (29.2)

*One subject 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

†One subject withdrew from the study to seek commercial therapy at week 162; 5 subjects withdrew between weeks 240 and 300: 2 due to meeting study stopping criteria (score of 0 in the combined motor-language domains at consecutive study visits) and 3 due to relocation or switch to commercial therapy

‡Common alleles are c.622C>T and c.509-1G>C

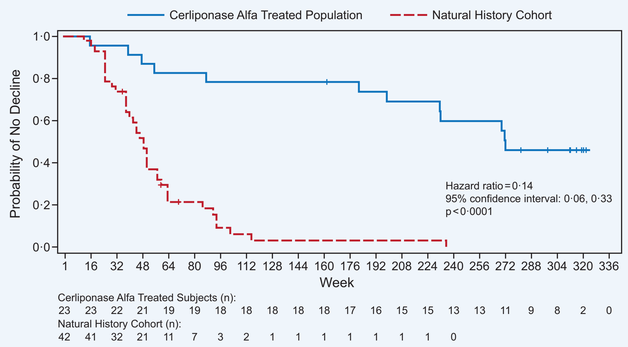
Study Drug Exposure

Study Drug Exposure, weeks at 300 mg dose	
Safety Population	N = 24
mean (SD)	260.8 (66.5)
min, max	0.1, 300.1
Efficacy Population (received >1 dose)	N = 23
mean (SD)	272.1 (37.4)
min, max	162.1, 300.1

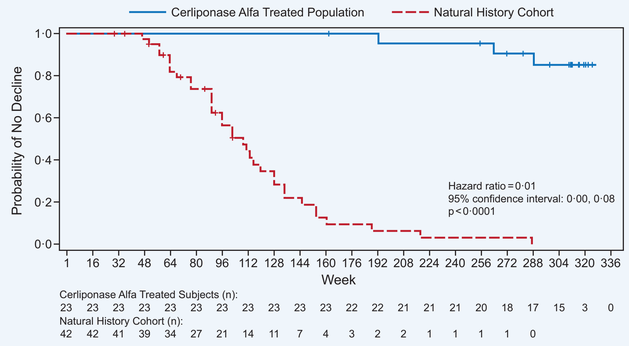
Time to 2-Point Decline or Score of 0 in Motor-Language Score

- Treated subjects were significantly less likely than natural history controls to have an unreversed 2-point decline or a score of 0 in the combined motor-language domains (Hazard Ratio [HR], 0.14; 95% confidence interval [CI], 0.06 to 0.33; p<0.0001).
- Treated subjects 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 (HR, 0.01; 95% CI, 0.00 to 0.08; p<0.0001).

Time to unreversed 2-point decline or score of 0 in motor-language domains



Time to unreversed score of 0 in motor-language domains



Rate of Decline in Motor-Language Score

- Rate of decline in motor-language score was significantly reduced among treated subjects compared to natural history controls.

Rate of Decline in ML Score (points per 48 weeks)	Natural History (N = 42)	190-201/202 (N = 23)	Difference
Mean (SD)	2.13 (0.95)	0.38 (0.50)	1.75
SE			0.18
Median (IQR)	2.08 (1.40, 2.80)	0.30 (0.15, 0.37)	
95% CI	1.84, 2.43	0.16, 0.59	0.39, 2.11

Change from Baseline in Total Cortical Gray Matter

- Among treated subjects, total gray matter volume declined by 13.5% from baseline to week 289; most of this decline occurred over the first 49 weeks of treatment.

Cortical Gray Matter Volume	Baseline	49 Weeks	97 Weeks	145 Weeks	193 Weeks	241 Weeks	289 Weeks
n	23	23	23	23	19	18	15
Percent change from Baseline	-	-9.7%	-12.8%	-13.4%	-15.5%	-12.9%	-13.5%
Annualized percent change from Baseline	-	-10.5%	-13.9%	-14.5%	-16.8%	-14.0%	-14.6%
Annualized interval percent change	-	-10.5%	-3.6%	-0.7%	-3.4%	+2.3%	+1.0%

Survival

- Treated subjects were significantly less likely to die than natural history controls (HR, 0.00; p < 0.0001). Median age of death was 10.4 years (95% CI, 9.5 to12.5) among natural history controls; there were no deaths among treated subjects (mean age at last dose, 10 years).

Safety Summary

- Cumulatively in 190-201/202, all subjects experienced at least 1 AE; most AEs were grade 1 or 2 in severity. All AEs resolved spontaneously or with appropriate medical management; 15 subjects 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.
- 240 AEs in 23 subjects were considered related to study drug; the most common drug-related AEs were pyrexia (127 events in 11 subjects), hypersensitivity (16 events in 10 subjects), seizure (14 events in 9 subjects), vomiting (15 events in 6 subjects), and epilepsy (4 events in 4 subjects).
- A total of 107 serious adverse events (SAEs) were reported in 21 subjects (88%).
  - 12 SAEs in 8 subjects were considered related to study drug; the most common drug-related SAEs were hypersensitivity (9 events in 7 subjects), infusion-associated reaction (2 events in 1 subject), pleocytosis (1 event in 1 subject).
- A total of 18 subjects (75%) had a total of 56 hypersensitivity AEs; 20 subjects (83%) experienced 72 device-related AEs; 23 subjects (96%) experienced 693 convulsion events (including 2 events of status epilepticus in 2 subjects); and 7 subjects (29%) experienced 15 cardiovascular events. No events of anaphylactic reaction, meningitis, hydrocephalus, or unexpected rapid motor-language score decline were reported.
- The proportion of subjects who reported ≥1 event of convulsions as an AE declined from 88% (n=21) during weeks 0-24 to 59% (n=13) in weeks >216.
- No association was found between serum anti-drug antibody titer and either incidence or severity of hypersensitivity adverse events and no association was found between CSF total antibody or neutralizing antibody titers and treatment outcome.

Common AEs	Overall (N = 24)
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%)
Body temperature increased	12 (50%)
Gait disturbance	12 (50%)
Cough	11 (46%)
Dystonia	11 (46%)
Tremor	11 (46%)
Visual impairment	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%)

Common SAEs	Overall (N = 24)
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 AEs shown are those reported in more than 35% of subjects; SAEs shown are those reported in more than 1 subject

Summary and Conclusions

- Over >5 years of treatment, ICV administration of 300 mg cerliponase alfa every 2 weeks in children with CLN2 disease slowed decline in motor and language function compared with untreated historical controls.
- Cerliponase alfa was generally well tolerated and had an acceptable safety profile; reported AEs were consistent with the known safety profile, the patient's underlying disease or concurrent conditions, and side effects of concurrent medications.
- Overall, these data indicate no change in the positive risk-benefit profile of cerliponase alfa.

References
1. Schulz et al. *N Engl J Med* 2018;378:1898-1907. **2.** Nickel et al. *Lancet Child Adolesc Health* 2018;2:582-590.

Acknowledgments
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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.

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