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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Disclosure Information
Angela Schulz, MD, PhD

- I have the following financial relationships to disclose:
  - Consultant: BioMarin Pharmaceutical Inc.
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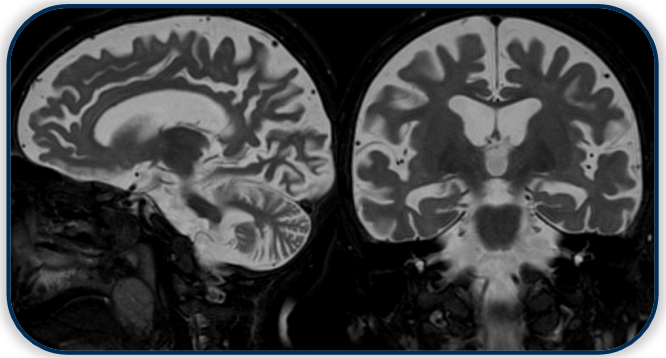
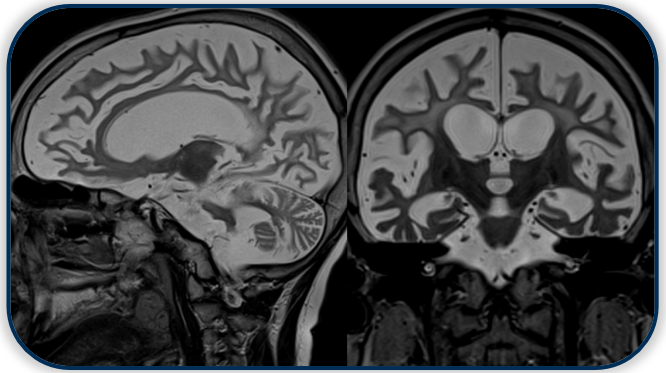
CLN2 Disease: A Form of Batten Disease

- CLN2 disease is an autosomal recessive form of neuronal ceroid lipofuscinosis (NCL)
  - most common group of neurodegenerative disorders in children and adolescents
  - share a core set of symptoms: seizures, progressive cognitive and motor deterioration, blindness, and premature death
- In CLN2 disease, deficiency in tripeptidyl peptidase (TPP1) enzyme leads to accumulation of lysosomal storage material, cell dysfunction, and death
- Symptom onset is typically at 2–4 years presenting with unprovoked seizures and history of language delay
- Rapid progressive neurodegeneration leads to early death



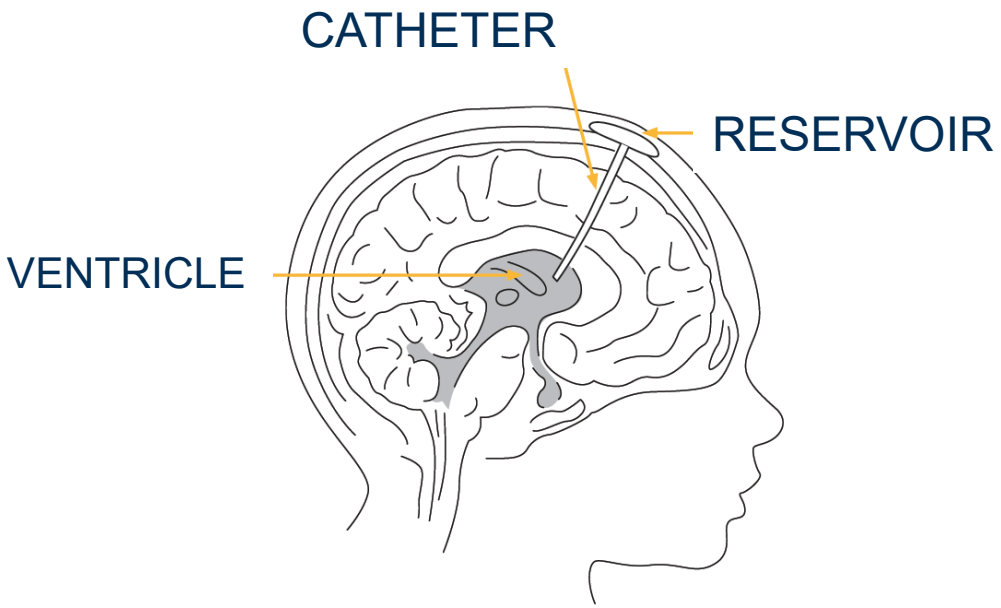
3.5 years



5 years

Cerliponase Alfa: Approved Therapy for CLN2 Disease

- Cerliponase alfa is a recombinant human form of TPP1 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

[1]Schulz et al. Study of intraventricular cerliponase alfa for CLN2 disease. *N Engl J Med* 2018; 378:1898-1907.

The CLN2 Clinical Rating Scale: Four Functional Domains

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

- 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

Primary Analysis

Supporting Analysis

Adapted from Steinfeld et al. *Am J Med Genet* 2002; 112:347-354.

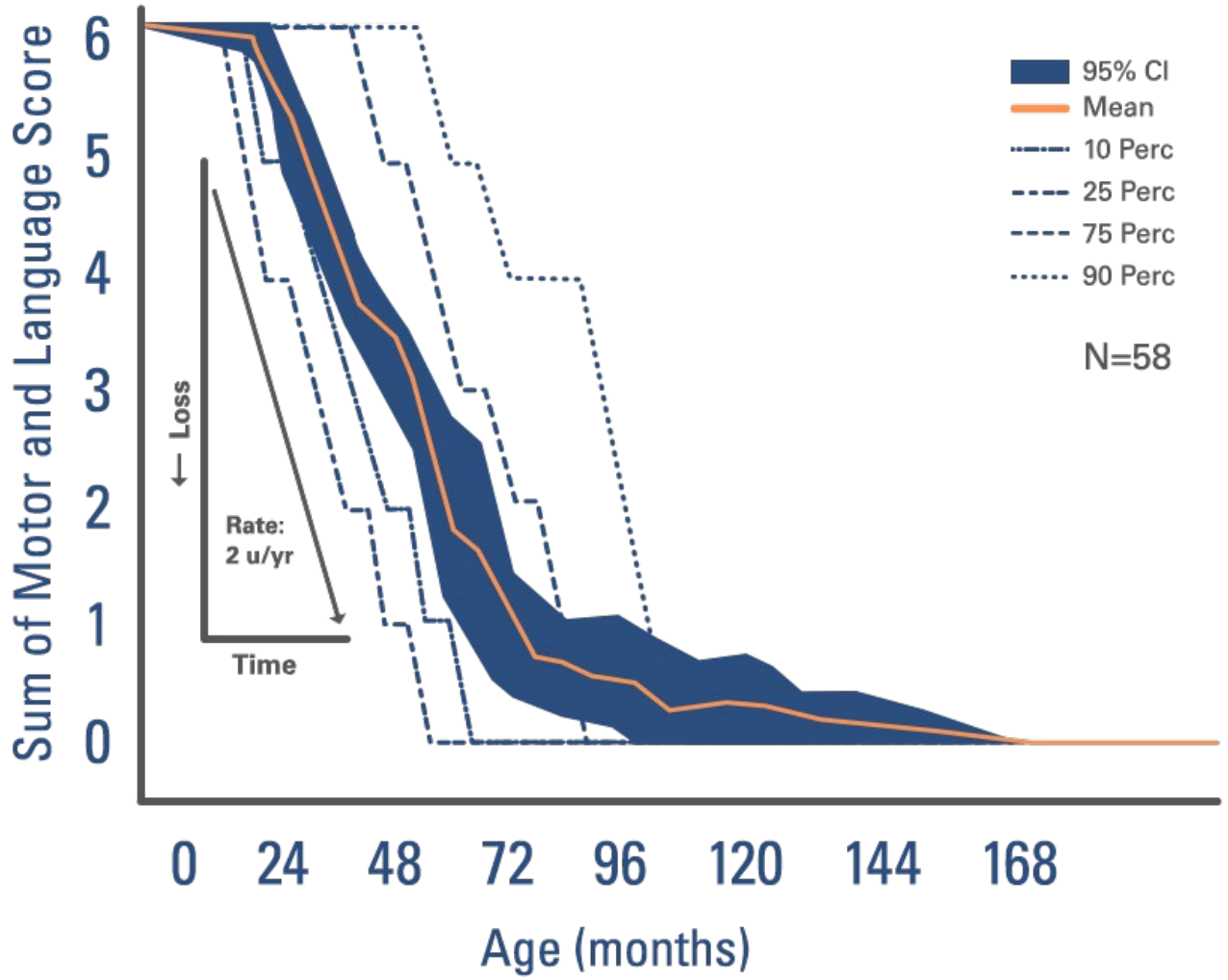
Natural History of CLN2 Disease: Decline in Motor-Language Score ~2 points/year

Clinical Score

MOTOR and LANGUAGE Assessments

	Score
Normal	3
Abnormal	2
Poor	1
No function	0

Sum of Motor & Language = **Max Score of 6**



DEM-CHILD

Study Objectives and Design

Study 190-203 Design

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

Primary study objectives

- Evaluate safety and tolerability of cerliponase alfa administered via intracerebroventricular (ICV) device
- Evaluate treatment effectiveness as a delay in progression of motor-language score on the Hamburg CLN2 clinical rating scale
- Assess immunogenicity of cerliponase alfa in cerebrospinal fluid and serum

Secondary study objectives

- Characterize the pharmacokinetics of cerliponase alfa in CSF and plasma
- 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 Inclusion criteria

- Diagnosis of CLN2 disease as determined by TPP1 enzyme activity
- Hamburg motor-language aggregate score 3–6 at Screening
- <18 years of age at the time of informed consent

Key Exclusion criteria

- 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)
- 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 first dose

https://clinicaltrials.gov/ct2/show/NCT02678689

Study Objectives and Design

Efficacy Evaluation

Primary efficacy endpoint is the rate of decline in score on motor and language domains of the CLN2 clinical rating scale

Treated subjects were matched to historical natural history controls (DEM-CHILD NCL database) on the basis of:

- **Age at baseline**: within 3 months
- **Genotype**: equal number of common alleles c.622C>T, c.509.1G
- **Baseline motor-language (ML) score**: exact match

https://clinicaltrials.gov/ct2/show/NCT02678689

Subject Demographics, Baseline Characteristics and Disposition

		190-203
Disposition, n (%) *as of current data cutoff (26 April 2020)*	Enrolled Treated Completed study Continuing on treatment Discontinued from study	14 (100.0%) 14 (100.0%) 10 (71.4%) 3 (21.4%) 1 (7.1%)
Age at enrollment, years	mean (SD), median min, max	3.0 (1.46), 2.6 0.9, 5.9
Age category, n (%)	< 3 years < 2 years	8 (57.1%) 5 (35.7%)
Sex, n (%)	Female Male	8 (57.1%) 6 (42.9%)
Baseline Motor-Language score, n (%)	6 5 4 3 2 1 mean (SD), median	7 (50.0%) 1 (7.1%) 3 (21.4%) 1 (7.1%) 1 (7.1%)* 1 (7.1%)** 4.6 (1.69), 5.5

*Subject had score of 3 at time of Screening

** Represents a subject with autism and uninterpretable language score

Subject Drug Exposure Summary

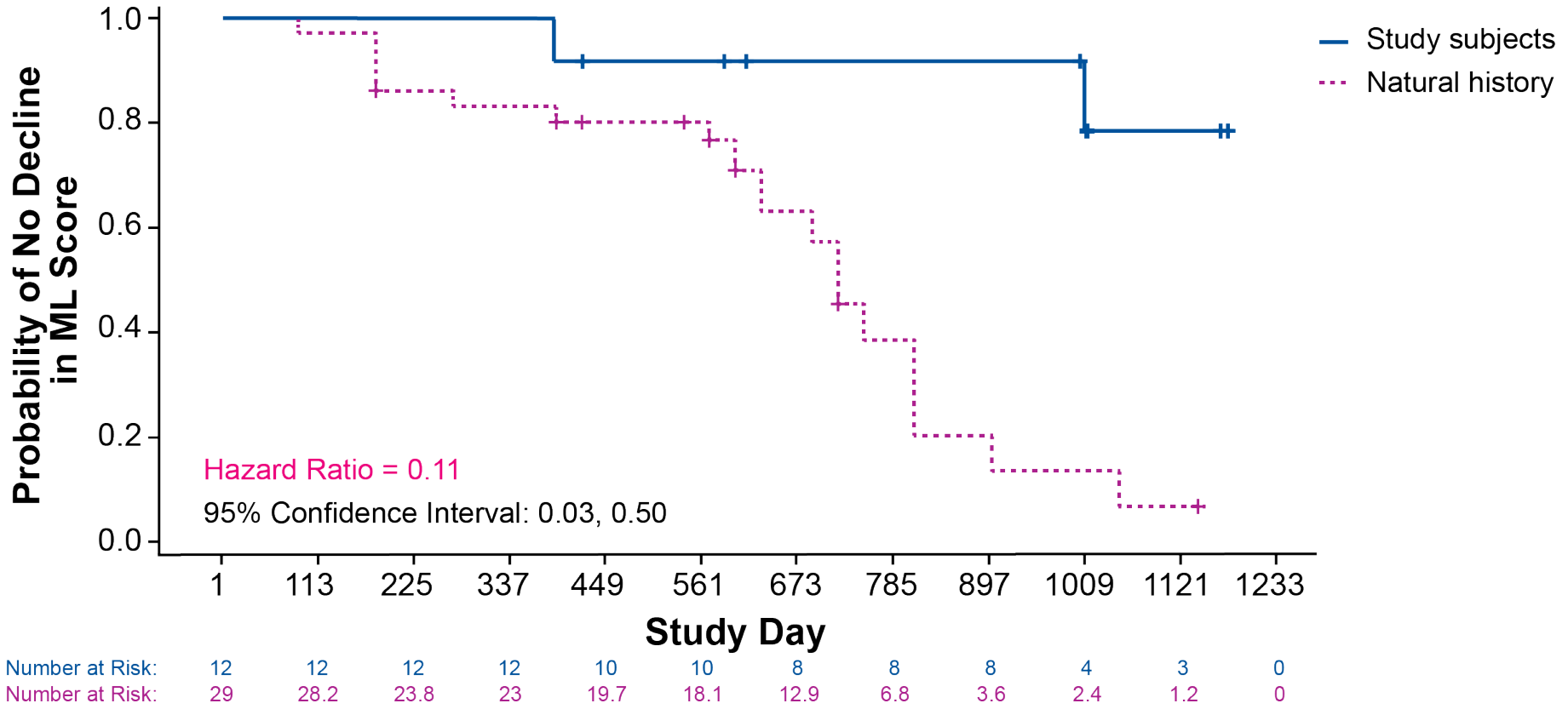
As of current data cutoff (26 April 2020)		**190-203** (N=14)
Study drug exposure, weeks	mean (SD) median range	127.0 (26.94) 141.9 64.4, 142.6
Total number of infusions	mean (SD) median range	64.1 (13.86) 72.0 31, 72

Rate of Decline in Motor-Language Score

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% Confidence Interval	0.85, 1.63	-0.03, 0.30	0.69, 1.52

- 12 out of 14 190-203 subjects met criteria for matching with evaluable natural history patients
- Mean (SD) baseline motor-language (ML) scores:
  - 5.0 (1.41) points in the matched 190-203 subjects
  - 5.0 (1.38) points in the natural history comparator cohort
- There was little decline in ML score in 190-203 subjects and a **greater than 1-point difference in rate of decline relative to matched natural history comparators**

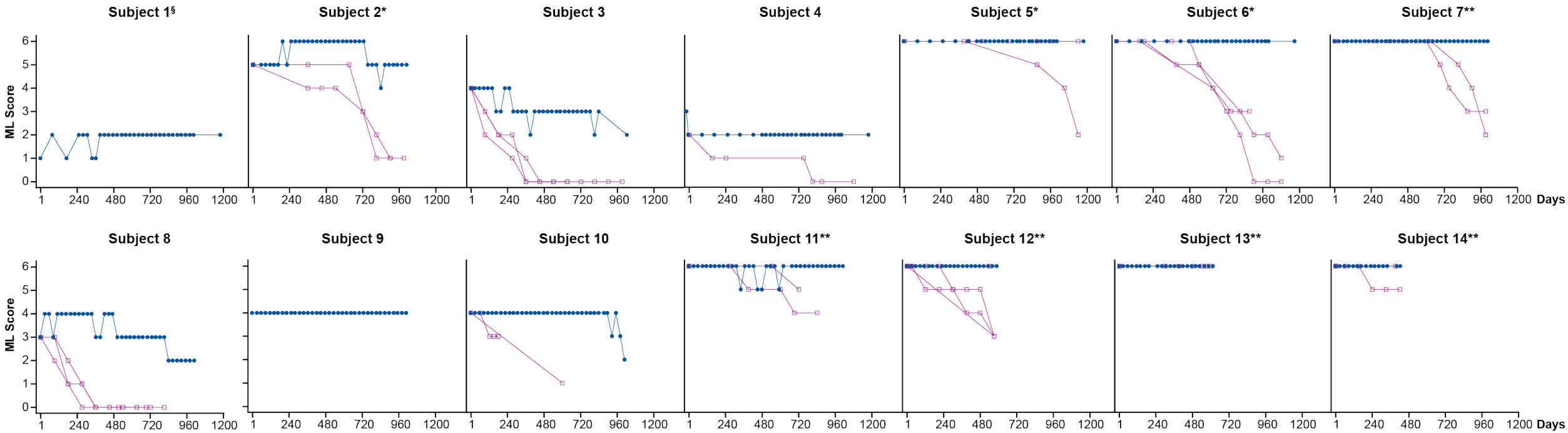
Time to 2-Point Decline in Motor-Language Score



Study Subjects Number at Risk:	12	12	12	12	10	10	8	8	8	4	3	0
Natural History Cohort Number at Risk:	29	28.2	23.8	23	19.7	18.1	12.9	6.8	3.6	2.4	1.2	0

- Cox proportional hazards model of time to unreversed 2-point decline in motor-language (ML) score or score of 0
  - **9-fold reduction in likelihood of ML decline** compared to matched natural history patients

Motor-Language Score Change from Baseline



190-203 study subject Natural history subject

Subjects 1 and 9 did not meet criteria for matching with evaluable natural history patients

§Subject with autism and uninterpretable language score

* age 2 to < 3 years at baseline ** age < 2 years at baseline

Adverse Event Summary

AE Summary [a]	Baseline Age (years)			Overall (N=14)
	< 2 (N=5)	<3 (N=8)	≥3 (N=6)	
Any AE, n (%)	5 (100%)	8 (100%)	6 (100%)	14 (100%)
Any AE Grade 1	5 (100%)	8 (100%)	6 (100%)	14 (100%)
Any AE Grade 2	5 (100%)	8 (100%)	6 (100%)	14 (100%)
Any AE Grade 3	3 (60%)	4 (50%)	5 (83%)	9 (64%)
Any AE Grade 4	0	0	1 (17%)	1 (7%)
AE Drug-Related, n (%)	5 (100%)	8 (100%)	3 (50%)	11 (79%)
Any SAE, n (%)	3 (60%)	6 (75%)	6 (100%)	12 (86%)

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

Common AEs [a,b]	Overall (N=14)
Pyrexia	12 (86%)
Upper respiratory tract infection	12 (86%)
Gastroenteritis	7 (50.%)
Extensor plantar response	6 (43%)
Generalized tonic-clonic seizure	6 (43%)
Hypersensitivity	5 (36%)
Speech disorder developmental	5 (36%)
Vomiting	5 (36%)

- Most adverse events (AEs) were Grade 1 or 2 in severity; 9 subjects experienced Grade 3 AEs (15 events); one subject had a Grade 4 AE of gastrointestinal fistula not related to study drug
- No deaths and no AEs resulting in permanent discontinuation of study drug
- No notable differences in the incidence of AEs between age subgroups

Serious Adverse Event Summary

SAEs	Overall (N=14)	SAEs	Overall (N=14)
Pyrexia	4 (29%)	Hypoxia	1 (7%)
Hypersensitivity	2 (14%)	Infection	1 (7%)
Influenza	2 (14.%)	Medical device hematoma	1 (7%)
Adenoidal hypertrophy	1 (7%)	Medical device site irritation	1 (7%)
Anaphylactic reaction	1 (7%)	Mycoplasma infection	1 (7%)
Cerebral disorder	1 (7%)	Periorbital hematoma	1 (7%)
Complications of device insertion	1 (7%)	Pneumonia	1 (7%)
Coronavirus infection	1 (7%)	Proprionibacterium test positive	1 (7%)
CSF cell count increased	1 (7%)	Pyelonephritis	1 (7%)
Dental caries	1 (7%)	Rhinitis	1 (7%)
Device leakage	1 (7%)	Rhinovirus infection	1 (7%)
Dysphagia	1 (7%)	Status epilepticus	1 (7%)
Escherichia urinary tract infection	1 (7%)	Upper respiratory tract infection	1 (7%)
Gastrointestinal fistula	1 (7%)	Viral infection	1 (7%)

- 40 serious adverse events (SAEs) 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)
  - dental caries (2 SAEs in 1 subject)
- 10 SAEs in 7 subjects were considered related to study drug:
  - pyrexia (7 events in 4 subjects)
  - hypersensitivity (2 events in 2 subjects)
  - anaphylactic reaction (1 event in 1 subject)

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)
  - Cohort includes 8 children < 3 years, 5 children < 2 years at baseline (age range: 0.9-5.9 years)
  - There were no adverse events resulting in permanent discontinuation of study drug
  - A new event of anaphylactic reaction was identified: 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**
  - Longer time on therapy is needed to assess impact on time to disease manifestation among younger patients

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