Improved Developmental Outcomes with Early Initiation of Cerliponase Alfa Treatment in Children with CLN2 Disease

Angela Schulz[1,2], Emily de los Reyes[3], Paul Gissen[4], Nicola Specchio[5], Kathleen Delaney[6], Jessica Cohen Pfeffer[6], Pascal Reisewitz[6]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2]German Center for Child and Adolescent Health, Partner Site Hamburg, Hamburg, Germany
[3]Nationwide Children's Hospital, Columbus, Ohio, USA
[4]NIHR Great Ormond Street Hospital Biomedical Research Centre, University College, London, UK
[5]Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[6]BioMarin Pharmaceutical Inc. Novato, California, USA

Conflicts of Interest Disclosures

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Background

- CLN2 disease is a rare neurodegenerative disease caused by deficient TPP1 enzyme activity[1–3]
- Affected children are functionally normal until seizures and delayed language acquisition emerge at 2 to 4 years of age, followed by rapid, progressive decline in motor, cognitive, language, and visual function[3,4]
- Cerliponase alfa (recombinant human tripeptidyl-peptidase 1 [rhTPP]) is currently the only disease-modifying therapy approved for the treatment of CLN2 disease
    - In previous studies, ICV administration of cerliponase alfa slowed decline in motor and language function in children with CLN2 disease, including those <3 years of age[4–6]
- The Denver II Developmental Scale is an instrument used in pediatric clinical practice to assess developmental skills in children from birth to 6 years of age, evaluating 125 age-appropriate tasks across four domains: fine motor, gross motor, language, and personal-social development[7]

This exploratory analysis evaluated developmental skills among children treated with cerliponase alfa in an expanded cohort including children <3 years of age (190-203; NCT02678689)

CLN2, ceroid lipofuscinosis type 2; ICV, intracerebroventricular; TPP1, tripeptidyl peptidase 1

1. Sleat et al. *Am J Hum Genet* 1999; 64:1511–23. **2.** Schulz et al. *Biochim Biophys Acta* 2013;1832:1801–6. **3.** Nickel et al. *Lancet Child Adolesc Health* 2018;2:582–90. **4.** Schulz et al. *N Engl J Med* 2018;378:1898–907. **5.** Schulz et al. *Lancet Neurol* 2024;23:60–70. **6.** Schulz et al. Poster P106 presented at the ILAE International Epilepsy Congress 2023. **7.** Frankenburg WK et al. *Pediatrics* 1992;89(1)91–7

Methods

190-203 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

Key inclusion criteria

- Diagnosis of CLN2 disease as determined by TPP1 enzyme activity
- Motor-language score 3–6 at screening
- <18 years of age at time of informed consent

Key exclusion criteria

- Other inherited neurologic disease or other neurologic 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

Exploratory outcome

- Developmental age-equivalent scores in each domain of the Denver II Developmental Scale were assessed at baseline and every 12 weeks until study completion

CLN2, ceroid lipofuscinosis type 2; TPP1, tripeptidyl peptidase 1

190-203 Study: 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)
Age, years	Mean (SD) Median (min, max)	3.1 (1.5) 2.7 (1.1, 6.0)
Age category, n (%)	<2 years ≥2 years	5 (36) 9 (64)
Motor-language score	Mean (SD) Median (min, max)	4.6 (1.7) 5.5 (1.0, 6.0)
Duration of treatment, weeks	Mean (SD)	140.4 (6.0)

[a]One patient discontinued the study to receive cerliponase alfa commercially
SD, standard deviation

190-203: Primary Efficacy Endpoint and Safety Data

Rate of decline in motor-language score

Rate of decline in motor-language score, points per 48 weeks	**Natural history controls** (n=29)	**Cerliponase alfa-treated patients** (n=12)
Mean (SD) **Median (min, max)**	**1.30** (0.86) 1.28 (0.00, 3.73)	**0.15** (0.24) 0.00 (0.00, 0.66)
	Mean difference: 1.15 95% CI: 0.80, 1.50; *P* < 0.0001	

Safety

n (%)	**Baseline age**			**Overall** N=14
	<2 years (n=5)	**<3 years** (n=9)	**≥3 years** (n=6)	
Any AE	**5 (100)**	**8 (100)**	**6 (100)**	**14 (100)**
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

- Rate of decline in motor-language score was significantly lower for cerliponase alfa-treated patients compared with matched untreated natural history controls
- All participants experienced at least 1 AE: most were mild or moderate in severity (Grade 1 or 2)

AE, adverse event; CI, confidence interval; SAE, serious adverse event; SD, standard deviation

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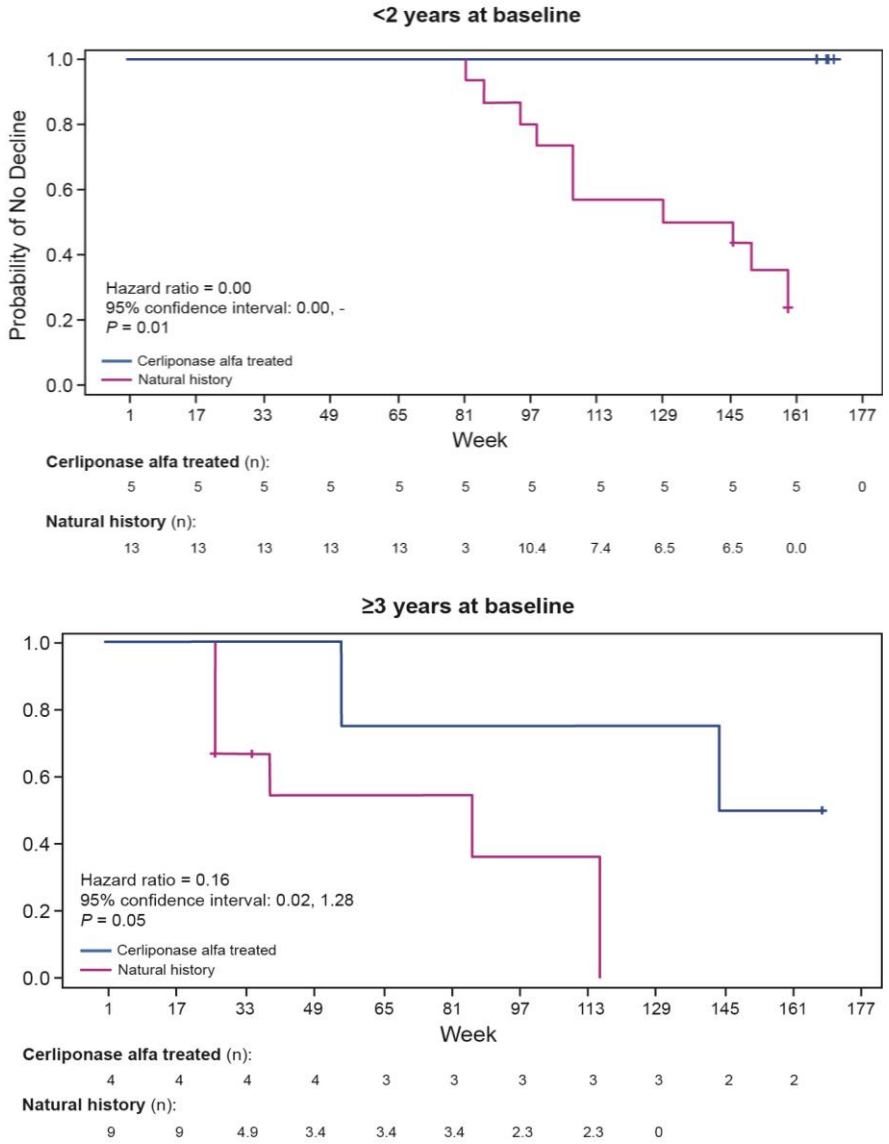
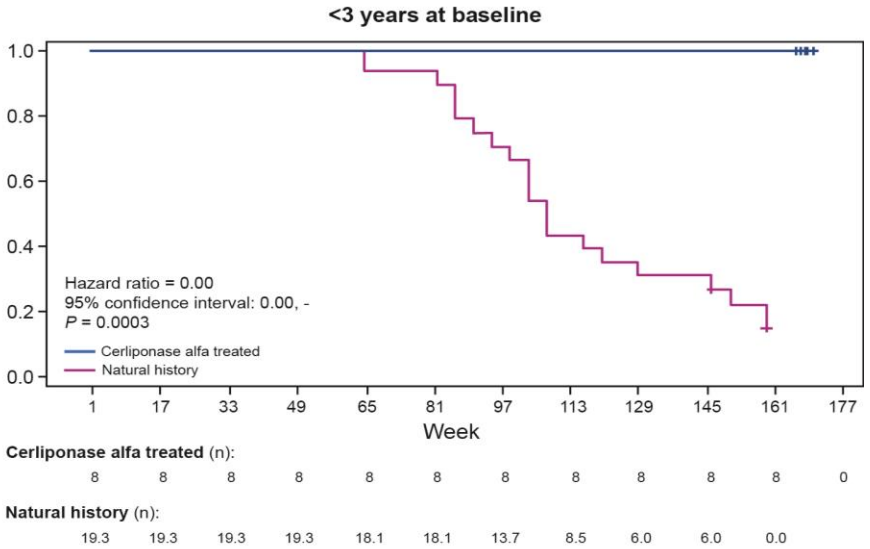
Time to unreversed 2-point decline or score of 0 in motor-language score





Treated patients <3 years of age at baseline did not experience an unreversed 2-point decline or score of 0 in motor-language score

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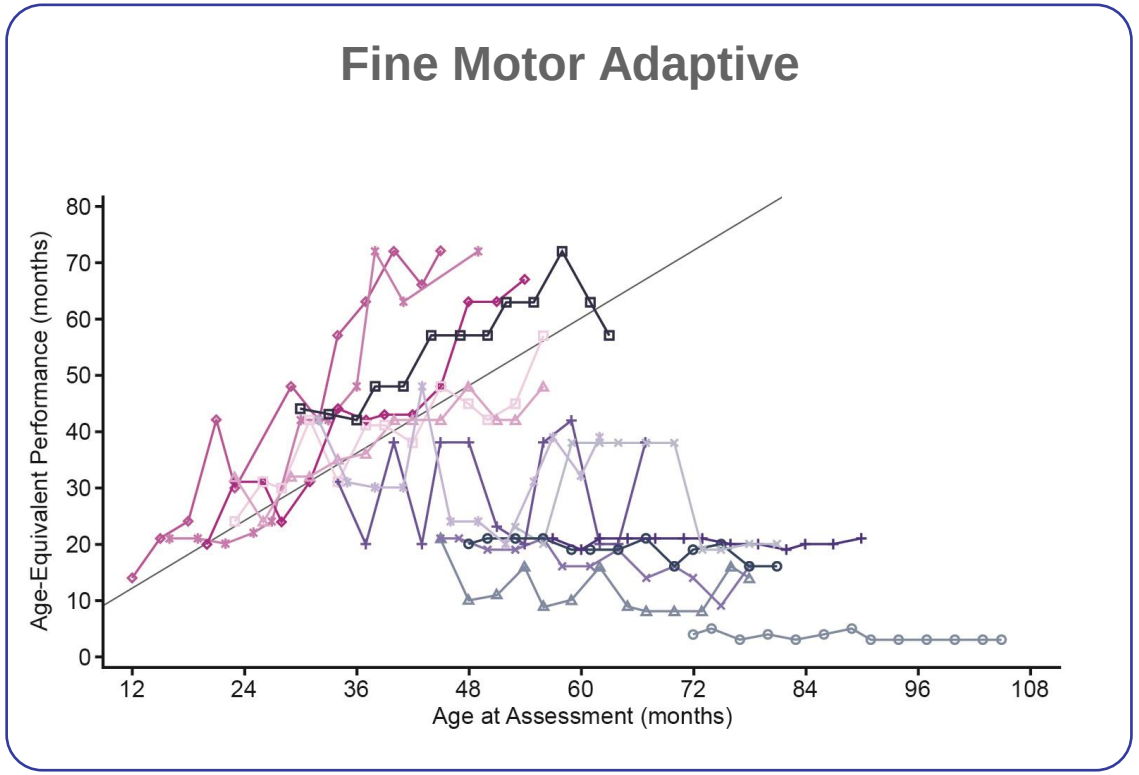
Denver II Development Scale: Baseline Age-Equivalent Scores

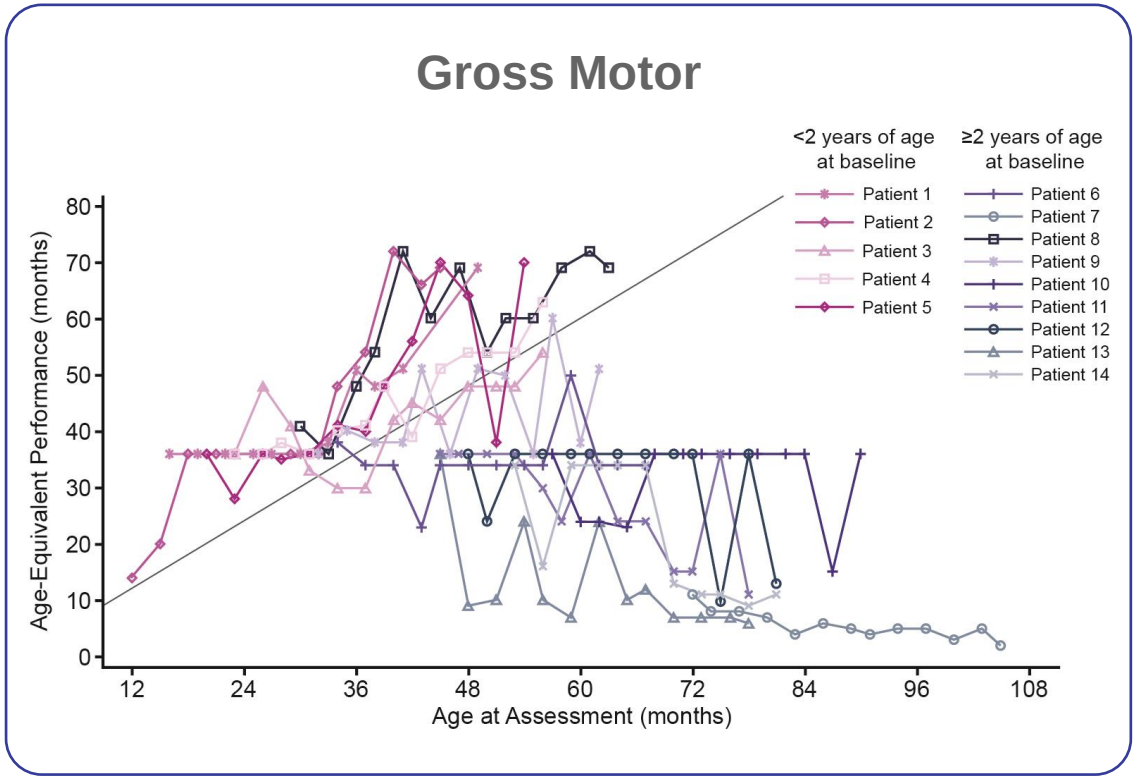
Baseline Denver II Developmental Scale age-equivalent scores, months, mean (SD)	**<2 years** (n=5)	**≥2 years** (n=9)
Fine motor adaptive	22.2 (6.6)	25.2 (12.3)
Gross motor	31.6 (9.8)	33.8 (8.8)
Language	25.6 (9.7)	31.3 (10.7)
Personal social	30.2 (8.1)	31.0 (15.3)

Among participants <2 years of age, most showed developmental age-equivalent scores at baseline that were at or above participant age at assessment

SD, standard deviation

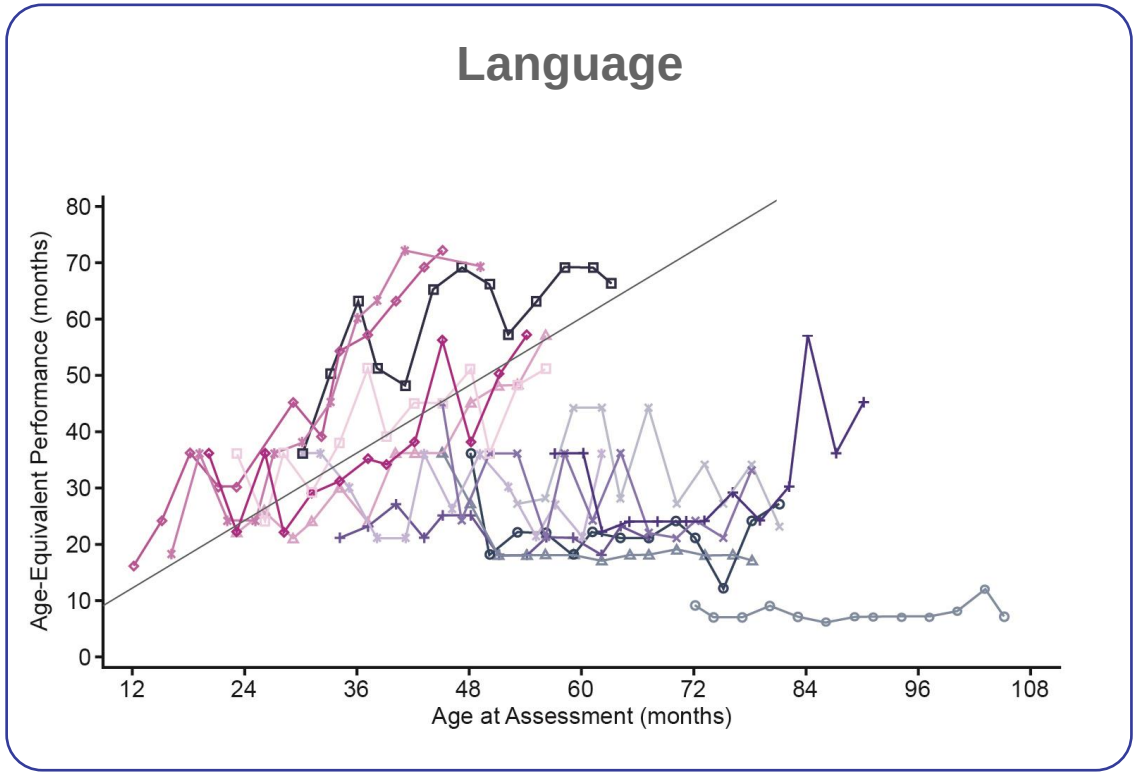
Individual Participant Outcomes for Denver Developmental Performance (1/2)

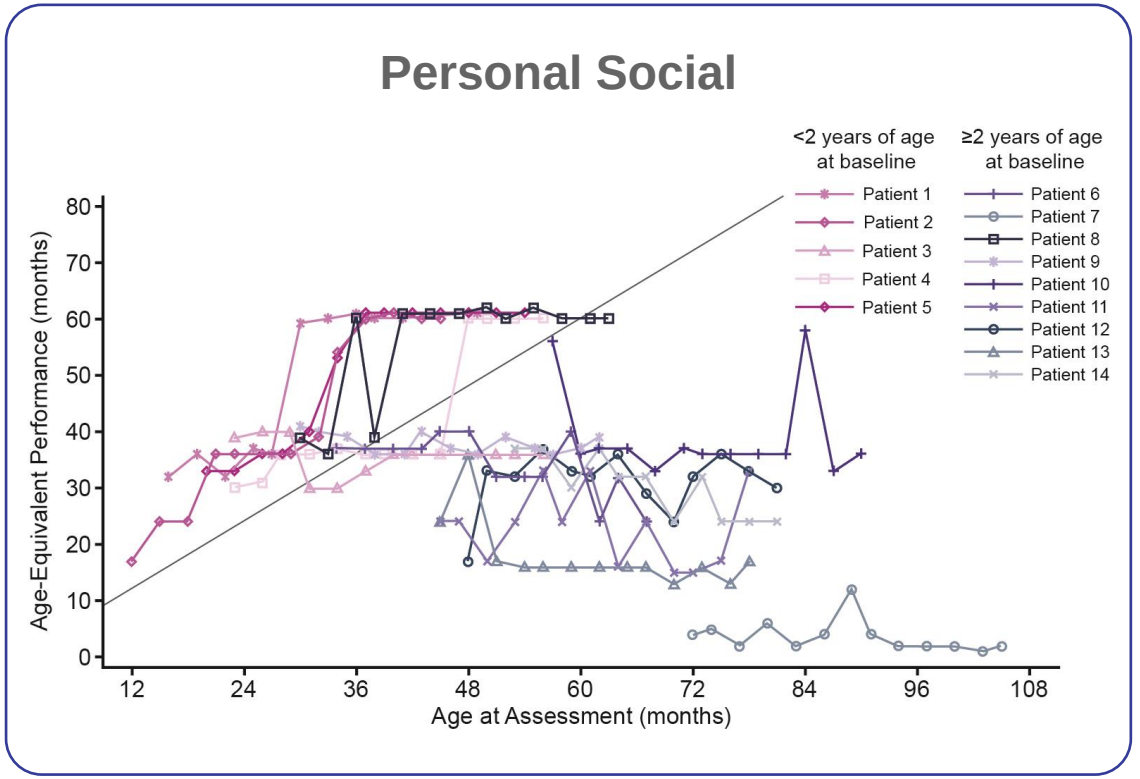




Diagonal line shows intersection between age-equivalent performance and age at assessment

Individual Participant Outcomes for Denver Developmental Performance (2/2)





Diagonal line shows intersection between age-equivalent performance and age at assessment

Change from baseline in Denver II Developmental Scale Age-Equivalent Scores

	Denver II Developmental Scale age-equivalent scores, months, mean (SD)			
	<2 years (n=5)		≥2 years (n=9)	
	Baseline	Change from baseline	Baseline	Change from baseline
Fine motor adaptive	22.2 (6.6)	+41.0 (16.7)	25.2 (12.3)	0.0 (6.7)
Gross motor	31.6 (9.8)	+33.4 (13.6)	33.8 (8.8)	–6.0 (20.3)
Language	25.6 (9.7)	+35.6 (18.0)	31.3 (10.7)	–0.4 (15.0)
Personal social	30.2 (8.1)	+25.4 (17.0)	31.0 (15.3)	–0.1 (13.7)

- Increases in mean (SD) scores were observed in all domains by study end among participants <2 years of age at baseline
- Participants ≥2 years showed little change across all domains over the study

SD, standard deviation

Conclusions

These results suggest age-appropriate attainment of developmental milestones in participants <2 years of age at baseline treated with cerliponase alfa

Early initiation of cerliponase alfa treatment, prior to typical age of symptom onset, may result in improved developmental outcomes in children with CLN2 disease

The Denver II scale compares children with age-matched norms; therefore, its applicability in CLN2 disease is limited, as affected children cannot be directly compared with the unaffected population

CLN2, ceroid lipofuscinosis type 2

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