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

413

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Introduction

- Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is a rare neurodegenerative disease caused by deficient tripeptidyl peptidase 1 (TPP1) enzyme activity[1–3]
- Symptoms typically first present between 2 and 4 years of age with seizures and language delay; symptom onset is followed by rapid, irreversible neurodegeneration, progressive decline in motor and language function, worsening epilepsy, and vision loss[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, intracerebroventricular (ICV) administration of cerliponase alfa slowed decline in motor and language function in children with CLN2 disease[4–6]
- Study 190-203 (NCT02678689, EudraCT 2015-000891-85) was an open-label, multicenter, 144-week study of cerliponase alfa in children <18 years of age with CLN2 disease
- We present findings from exploratory analyses assessing the attainment of developmental milestones among children treated with cerliponase alfa in the 190-203 study

Conclusions

- Children with CLN2 disease who initiated cerliponase alfa treatment before 2 years of age in the 190-203 study showed age-appropriate attainment of developmental milestones over 3 years of follow-up
  - While study participants who initiated treatment at ≥2 years did not substantially achieve new developmental milestones or regain lost milestones, they did maintain stable scores with minimal decline
- Early initiation of cerliponase alfa treatment, prior to the typical age of symptom onset, may result in improved developmental outcomes in children with CLN2 disease

Methods

190-203 study design

- The 190-203 study was conducted between 2016 and 2022 across 4 tertiary care hospitals in Germany, Italy, the US, and the UK
- Eligible participants were aged <18 years with confirmed diagnosis of CLN2 disease and a score of between 3 and 6 on the combined motor and language domains of the CLN2 Clinical Rating Scale at screening
- Participants received ICV cerliponase alfa biweekly for at least 144 weeks, followed by an additional 48 week safety follow-up period
- The primary efficacy outcome was rate of decline in score on the motor and language domains of the CLN2 Clinical Rating Scale compared with matched natural history controls
- Exploratory outcomes included developmental age-equivalence scores, assessed via the Denver II Developmental Screening Test at baseline and every 12 weeks until study completion

Denver II Developmental Screening Test

- The Denver II Developmental Screening Test is a standardized instrument used to screen children from birth to 6 years of age for possible developmental delays[7]
- Denver II allows the comparison of a child's performance on a set of up to 125 age-appropriate tasks to normative data from same-age peers, across four domains:
  - Personal-Social (interaction with people, self-care skills, and emotional responses)
  - Fine Motor-Adaptive (hand-eye coordination, grasping, and manipulative skills)
  - Language (receptive and expressive communication)
  - Gross Motor (large muscle development such as sitting, walking, running, and jumping)
- Developmental age-equivalence scores were derived for each Denver II item based on the age at which 50% of children in the standardization sample passed the item. Domain-level age-equivalence scores were then calculated as the mean of the item-specific age equivalence scores within the domain

Results

Table 1. Demographics and baseline characteristics

	N=14
Sex, n (%)	
Male	6 (43)
Female	8 (57)
Age, years	
Mean (SD)	3.1 (1.5)
Median (min, max)	2.7 (1.1, 6.0)
Age category, n (%)	
<2 years	5 (36)
≥2 years	9 (64)
Motor–language score	
Mean (SD)	4.6 (1.7)
Median (min, max)	5.5 (1.0, 6.0)

SD, standard deviation.

Study Participants

- 14 participants were enrolled in the study (**Table 1**)
  - One participant discontinued the study by choice after 146 weeks (during the 24-week safety follow-up period) but continued cerliponase alfa treatment outside of the trial setting
  - Mean (SD) treatment duration was 140.4 (5.96) weeks

Primary Efficacy

- The rate of decline in motor–language score was significantly lower for cerliponase alfa treated patients than matched untreated natural history controls[6]
- Participants who initiated treatment before 3 years of age, typically prior to symptom appearance, did not experience an unreversed 2-point decline or score of 0 in motor–language score by end of follow up (**Figure 1**)

Safety

- All participants experienced at least 1 adverse event; most were mild or moderate in severity (Grade 1 or 2)
- The were no deaths and no adverse events resulted in treatment discontinuation

Denver II Developmental Screening Test Outcomes

- Among participants who initiated treatment at <2 years of age, most showed age-equivalent performance on each of the 4 domains of the Denver II Developmental Screening Test at baseline that aligned with their chronological age, and continued to show age-appropriate attainment of developmental skills throughout the study (**Figure 2**)
- In contrast, participants who initiated treatment at ≥3 years of age had baseline age-equivalent performance below their chronological age and showed little change over study follow up

Figure 1. Time to unreversed 2-point decline or score of 0 in motor–language score

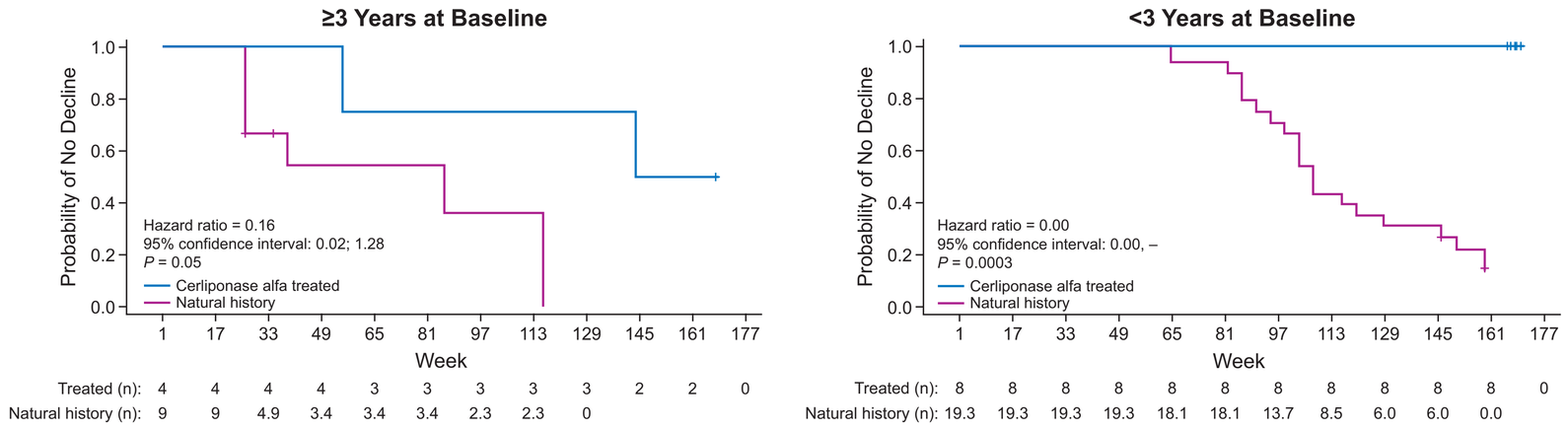
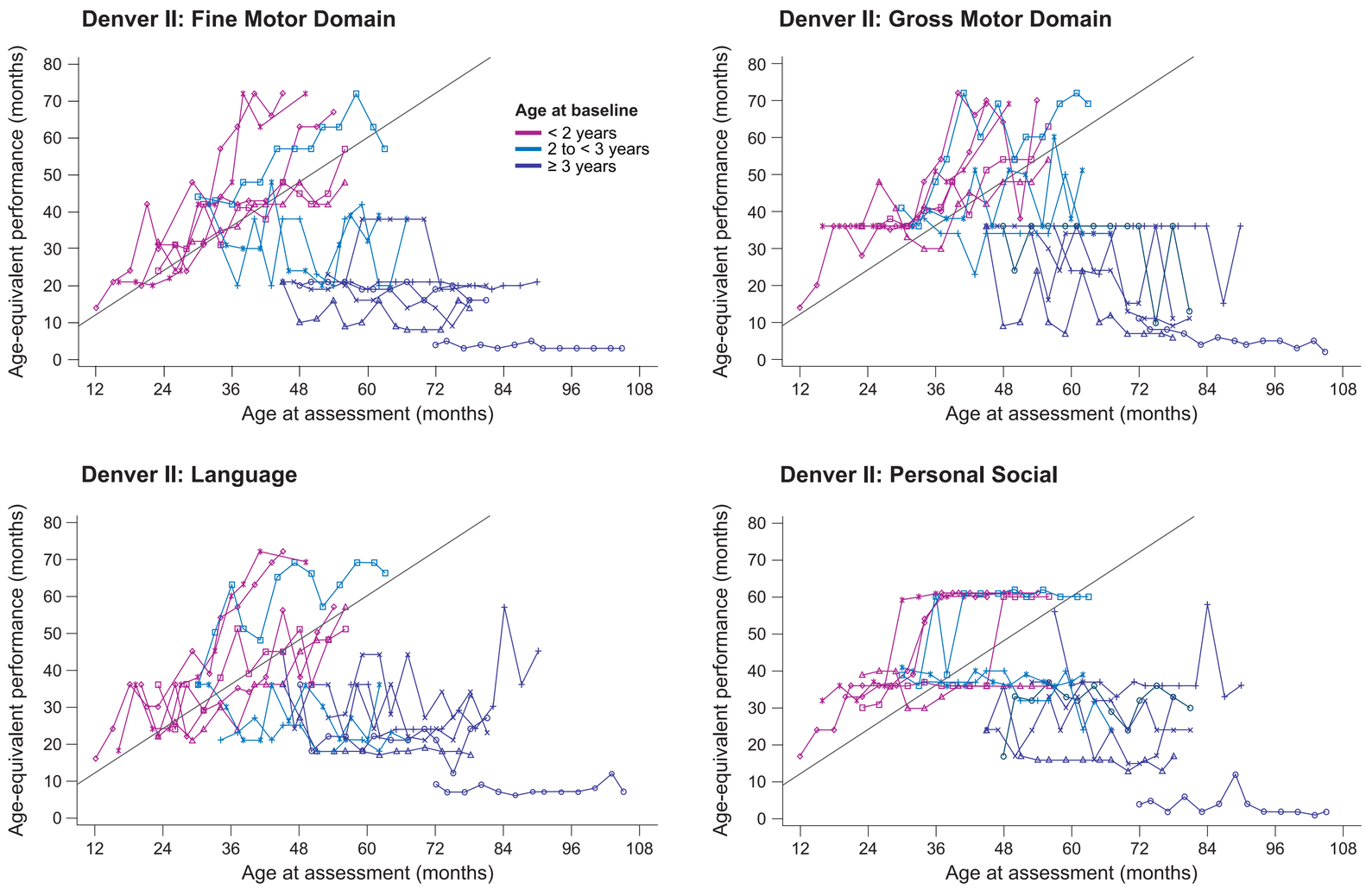


Figure 2. Individual developmental outcomes among cerliponase alfa-treated participants (Denver II)



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Disclosures

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