# Real-world clinical outcomes of intraventricular cerliponase alfa in CLN2 disease: Comparison with a historical cohort

Angela Schulz[1], Christoph Schwering[1], Eva Wibbeler[1], Lena M Westermann[1], Luca Hagenah[1], Susanne Lezius[2], Peter Slasor[3], Pascal Reisewitz[3], Miriam Nickel[1]

*[1]Children's Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Department of Biometrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]BioMarin Pharmaceutical Inc., Novato, CA, USA*

# Conflict of interest disclosure

- **Angela Schulz** has received research grants from BioMarin Pharmaceutical Inc.; honoraria for speaker fees from BioMarin Pharmaceutical Inc., and for consultations from Regenxbio Inc. and Neurogene Inc.; and was Principal Investigator in the BMN 190 clinical trials funded by BioMarin Pharmaceutical Inc.

# CLN2 disease: A rare and rapidly progressive childhood neurodegenerative disorder

CLN2 disease is a rare, genetic, neurodegenerative disorder of childhood caused by deficient tripeptidyl peptidase 1 (TPP1) enzyme activity[1–3]

Deficient TPP1 activity results in the intralysosomal accumulation of autofluorescent storage material and subsequent neuronal and retinal cell loss[1,2]

Symptom onset of classic late-infantile phenotype is typically at 2–4 years of age, presenting with unprovoked seizures and history of language delay followed by psychomotor decline and vision loss[1–3]

Neurodegeneration is rapidly progressive, leading to early death[1–3]

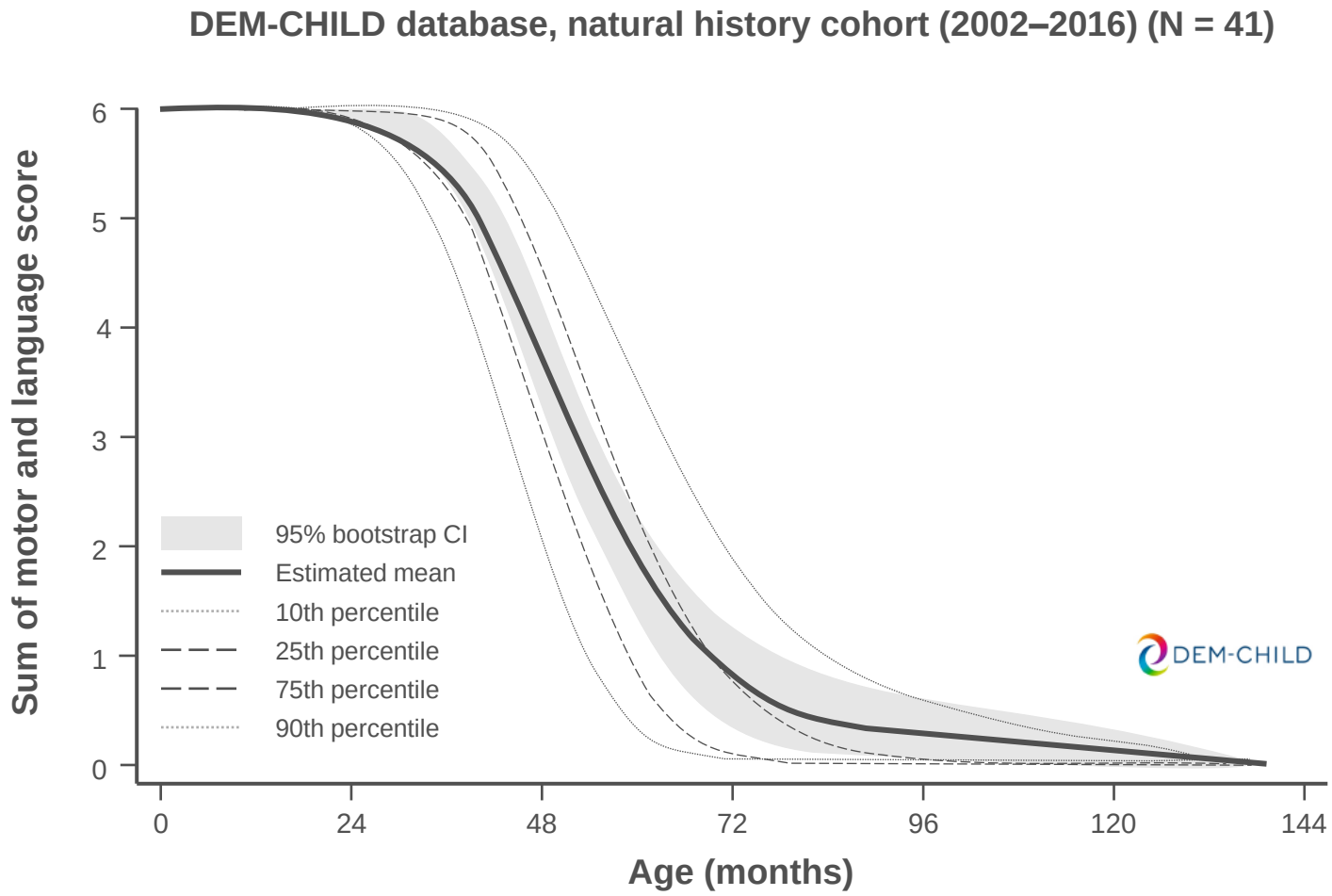


CLN2, neuronal ceroid lipofuscinosis type 2; TPP1, tripeptidyl peptidase 1.

1. Schulz A, et al. Annual World Symposium 2022 [Poster LB-63];
2. Gardner E, et al. *Hum Mutat*. 2019;40:1924–38;
3. Schulz A, et al. *N Engl J Med*. 2018;378:1898–907.

# CLN2 disease is associated with rapid decline in motor and language function

**Motor and language domains** are each scored from 3 to 0, with lower scores indicating more extensive impairment of function




CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; DEM-CHILD, A Treatment-Oriented Research Project of NCL Diseases as a Major Cause of Dementia in Childhood; NCL, neuronal ceroid lipofuscinosis.

Adapted from Nickel M, et al. *Lancet Child Adolesc Health*. 2018;2:582–90.

# Cerliponase alfa

- Cerliponase alfa is a recombinant human form of TPP1 enzyme and was approved for the treatment of CLN2 disease in the US and EU in 2017[1–4]
  - In clinical trials, intracerebroventricular administration of cerliponase alfa was shown to slow decline in motor and language function compared to natural history[1,2]

Study objective:
To assess the real-world effectiveness and safety of cerliponase alfa in children with CLN2 disease who initiated treatment outside of the clinical trial setting using data from the independent DEM-CHILD database (international NCL patient registry)

CLN2, neuronal ceroid lipofuscinosis type 2; DEM-CHILD, A Treatment-Oriented Research Project of NCL Diseases as a Major Cause of Dementia in Childhood; NCL, neuronal ceroid lipofuscinosis; TPP1, tripeptidyl peptidase 1.

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3. Brineura. Highlights of Prescribing Information. March 2020. Available at: https://www.brineura.com/wp-content/themes/jupiter-child/assets/pdfs/resources/Brineura-Prescribing-Information.pdf;
4. Brineura. SmPC. August 2022. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/brineura.

# Analysis methods

## Patients

- Enrolled in the DEM-CHILD database (international NCL patient registry) (NCT04613089) with confirmed diagnosis of CLN2 disease by genetic and enzyme testing

  **Treated patients**: initiated cerliponase alfa outside of clinical trials and had at least 6 months of follow-up on treatment

  **Natural history patients**: never received cerliponase alfa

## Matching

- Treated patients were matched 1:1 with natural history patients on:
  - Baseline[a] age (±12 months) AND
  - Baseline score on motor and language (ML) domains (exact match)

## Follow-up

- Data were considered from baseline until end of follow-up or data cut-off (December 30, 2020) for treated patients, and for period equivalent to that of the matched treated patient for natural history patients

## Outcomes of interest

- Rate of decline in ML score
- Time to unreversed 2-point decline or ML score of 0
- Treatment-related adverse events

[a]Baseline was defined as the last observation prior to the first dose (treated patients), or assessment at the age of matching (natural history patients).
CLN2, neuronal ceroid lipofuscinosis type 2; DEM-CHILD, A Treatment-Oriented Research Project of NCL Diseases as a Major Cause of Dementia in Childhood; ML, motor-language; NCL, neuronal ceroid lipofuscinosis.

# Patient characteristics

## Patients matched on baseline age and ML score

| | | Natural history N = 21 | Cerliponase alfa-treated N = 21 |
|---|---|---|---|
| **Sex** | n (%) | | |
| Female | | 5 (24) | 11 (52) |
| Male | | 16 (76) | 10 (48) |
| **Age at baseline**, years | Mean (SD) | 4.7 (1.9) | 4.7 (1.9) |
| | Median [min, max] | 4.5 [0.7, 9.9] | 4.5 [0.7, 9.9] |
| **Baseline ML score** | Mean (SD) | 3.9 (1.6) | 3.9 (1.6) |
| | Median [min, max] | 4 [1, 6] | 4 [1, 6] |
| **Baseline ML score category** | n (%) | | |
| 1 | | 1 (5) | 1 (5) |
| 2 | | 4 (19) | 4 (19) |
| 3 | | 3 (14) | 3 (14) |
| 4 | | 6 (29) | 6 (29) |
| 5 | | 2 (10) | 2 (10) |
| 6 | | 5 (24) | 5 (24) |
| **Genotype** | n (%) | | |
| 2 common alleles[a] | | 13 (62) | 14 (67) |
| 1 common allele | | 5 (24) | 4 (19) |
| 0 common alleles | | 3 (14) | 3 (14) |
| **Age at disease onset**, years | | | n = 20 |
| | Mean (SD) | 3.0 (0.8) | 3.4 (0.8) |
| | Median [min, max] | 3.0 [1.3, 4.4] | 3.3 [2.1, 6.0] |
| **Age at diagnosis**, years | | n = 17 | |
| | Mean (SD) | 5.2 (1.6) | 4.2 (2.0) |
| | Median [min, max] | 4.8 [2.9, 9.8] | 3.9 [0.2, 8.8] |

[a]The common alleles are c.622C>T and c.509-1G>C.

max, maximum; min, minimum; ML, motor-language; n, number of valid observations; N, number of patients; SD, standard deviation.

# Rate of decline in ML score

## Patients matched on baseline age and ML score

| | Natural history N = 21 | Cerliponase alfa-treated N = 21 |
|---|---|---|
| **Rate of decline in ML score**, points per 48 weeks | | |
| Mean (SD) | **1.88** (1.45) | **0.46** (0.43) |
| Median [min, max] | 1.66 [0.00, 5.60] | 0.44 [0.00, 1.33] |
| 95% CI | 1.22, 2.54 | 0.26, 0.64 |

**Mean (SE) difference: 1.42 (0.33)**
95% CI: 0.74, 2.10; p = 0.0003

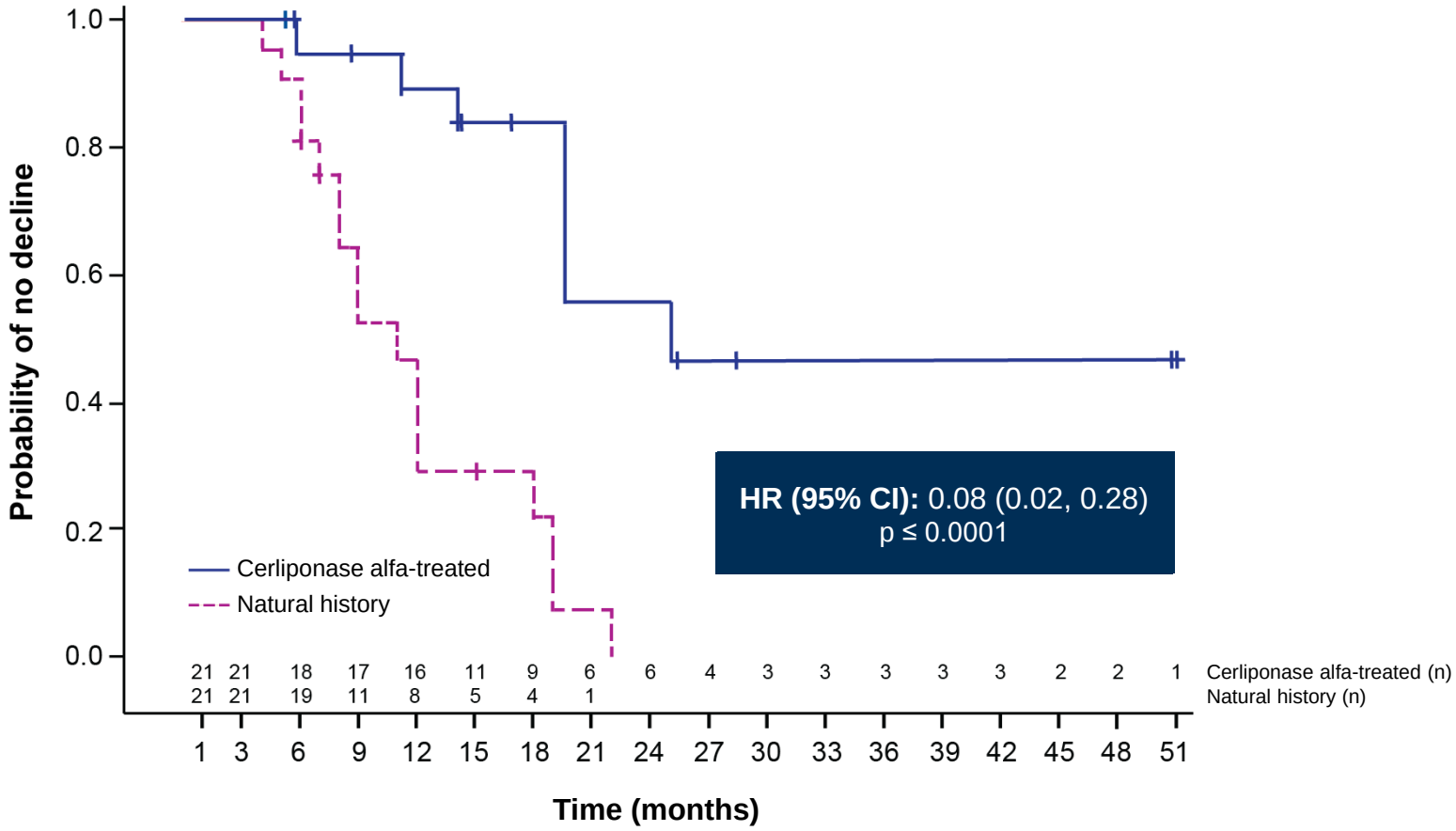
- At the end of follow-up, cerliponase alfa-treated patients had:
  - Higher ML score than matched natural history controls in 15/21 pairs (71%)
  - Equivalent ML score to matched natural history controls in 6/21 pairs (29%)



CI, confidence interval; max, maximum; min, minimum; ML, motor-language; N, number of patients; SD, standard deviation; SE, standard error.

# Time to unreversed 2-point decline or score 0 in ML domains

**Patients matched on baseline age and ML score**




CI, confidence interval; HR, hazard ratio; ML, motor-language; n, number of valid observations.

# Treatment-related adverse events

## All cerliponase alfa-treated patients (N = 24)

| | All treatment-related AEs N = 24 | | | Treatment-related AEs resulting in hospitalization N = 24 | | |
|---|---|---|---|---|---|---|
| | **Incidence** n (%) | **Events** | **Rate** (events/100 PY) | **Incidence** n (%) | **Events** | **Rate** (events/100 PY) |
| **Any treatment-related AE** | 16 (66.7) | 75 | 13.4 | 7 (29.2) | 19 | 3.4 |
| **Treatment-related AEs** | | | | | | |
| Pyrexia | 12 (50.0) | 43 | 7.7 | 4 (16.7) | 5 | 0.9 |
| Vomiting | 8 (33.3) | 10 | 1.8 | 5 (20.8) | 6 | 1.1 |
| Nausea | 5 (20.8) | 5 | 0.9 | 2 (8.3) | 2 | 0.4 |
| Arrythmia | 3 (12.5) | 3 | 0.5 | 0 | 0 | 0 |
| Device-related infection | 3 (12.5) | 3 | 0.5 | 3 (12.5) | 3 | 0.5 |
| Seizure | 3 (12.5) | 6 | 1.1 | 0 | 0 | 0 |
| Device leakage | 2 (8.3) | 2 | 0.4 | 2 (8.3) | 2 | 0.4 |
| Flushing | 1 (4.2) | 2 | 0.4 | 0 | 0 | 0 |
| Headache | 1 (4.2) | 1 | 0.2 | 1 (4.2) | 1 | 0.2 |

There were no deaths in the cerliponase alfa-treated group; 6 (29%) patients in the natural history control group died during the equivalent length of follow-up (median time to death: 313 weeks)



AE, adverse event; n, number of valid observations; N, number of patients; PY, patient-years.

# Conclusions

- Cerliponase alfa treatment slowed deterioration in motor and language function in children with CLN2 disease in a real-world setting
  - These results from the real-world setting support efficacy findings from cerliponase alfa clinical trials
- No new safety signals were identified
  - Treatment-related AEs observed were consistent with those seen in clinical trials
- Study limitations:
  - Historical controls
  - Only AEs suspected by the treating physician to be treatment (drug or device)-related were considered



AE, adverse event; CLN2, neuronal ceroid lipofuscinosis type 2.

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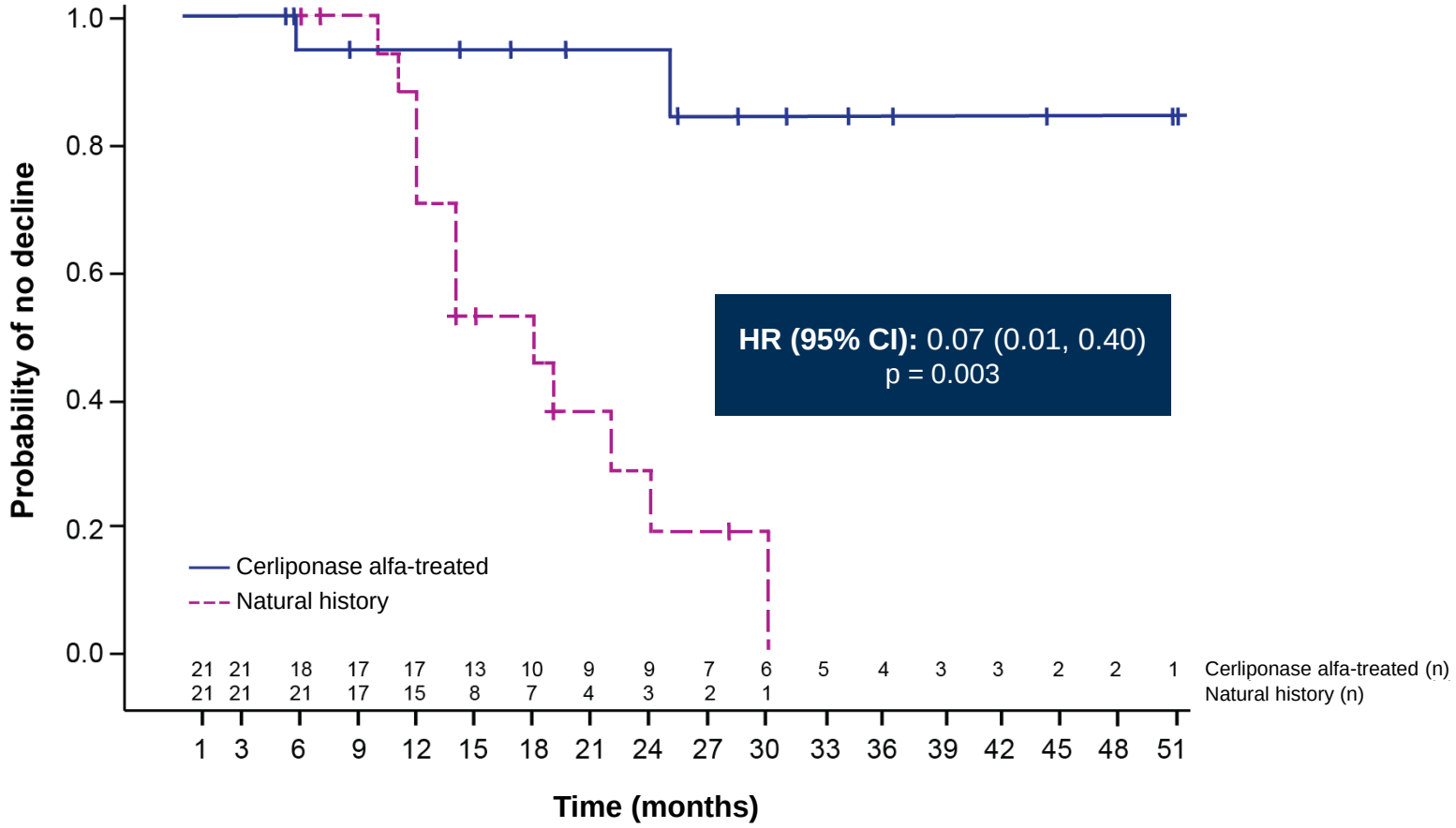
# Time to unreversed score of 0 in ML domains

## Patients matched on baseline age and ML score






CI, confidence interval; HR, hazard ratio; ML, motor-language; n, number of valid observations.

# Rate of decline in motor score

## Patients matched on baseline age and ML score

| | | Natural history<br>N = 21 | Cerliponase alfa-treated<br>N = 21 |
|---|---|---|---|
| **Rate of decline in motor score**, points per 48 weeks | | n = 20 | n = 20 |
| | Mean (SD) | **0.99** (0.75) | **0.23** (0.28) |
| | Median [min, max] | 1.02 [0.00, 2.40] | 0.11 [0.00, 0.79] |
| | 95% CI | 0.64, 1.34 | 0.10, 0.36 |

**Mean (SE) difference: 0.75 (0.18)**
95% CI: 0.38, 1.12; p = 0.0003

CI, confidence interval; max, maximum; min, minimum; ML, motor-language;
n, number of valid observations; N, number of patients; SD, standard deviation; SE, standard error.

# Rate of decline in language score

## Patients matched on baseline age and ML score

| | | Natural history<br>N = 21 | Cerliponase alfa-treated<br>N = 21 |
|---|---|---|---|
| **Rate of decline in language score**, points per 48 weeks | | n = 19 | n = 18 |
| | Mean (SD) | **1.04** (0.96) | **0.16** (0.28) |
| | Median [min, max] | 0.80 [0.00, 3.73] | 0.00 [0.00, 0.72] |
| | 95% CI | 0.58, 1.50 | 0.02, 0.30 |

**Mean (SE) difference: 0.88 (0.23)**
95% CI: 0.40, 1.36; p = 0.001

CI, confidence interval; max, maximum; min, minimum; ML, motor-language;
n, number of valid observations; N, number of patients; SD, standard deviation; SE, standard error.

# Sensitivity analysis: Rate of decline in ML score

## Patients matched on baseline age, ML score, and genotype (3-criteria match)

| | | Natural history<br>N = 18 | Cerliponase alfa-treated<br>N = 18 |
|---|---|---|---|
| **Rate of decline in ML score**, points per 48 weeks | | | |
| | Mean (SD) | **2.07** (1.61) | **0.49** (0.43) |
| | Median [min, max] | 2.18 [0.00, 5.60] | 0.47 [0.00, 1.33] |
| | 95% CI | 1.27, 2.87 | 0.28, 0.70 |

**Mean (SE) difference: 1.58 (0.39)**
95% CI: 0.76, 2.40; p = 0.0007

CI, confidence interval; max, maximum; min, minimum; ML, motor-language; N, number of patients; SD, standard deviation; SE, standard error.