# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12)

For Zoom –CON and DPD information redacted

**Highly Specialized Technology Appraisal Committee [3rd April 2025]**

**Chair:** Paul Arundel

**External assessment group:** CRD and CHE Technology Assessment Group, University of York

**Technical team:** Ross Wilkinson, Joanna Richardson, Richard Diaz

**Company:** BioMarin Pharmaceuticals





Abbreviations: CON, Confidential; DPD, Depersonalised data; HST, Highly specialised technology;

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12)

- ✓ **Recap of ACM1 and ACM2**
- ❑ Key Issues
- ❑ Cost effectiveness

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# History of the appraisal

| | |
|---|---|
| **November 2019 MA Entry (HST12)** | • Cerliponase alfa received a positive recommendation within the context of a MAA<br>• The previous appraisal identified several issues that meant that a MAA was needed<br>↳ These included limited evidence and uncertainties in several areas |
| **MA-review** | • This HST represents a new review of cerliponase alfa focusing on the existing evidence and the new evidence generated since the previous HST |
| **ACM1** | • After ACM1 committee asked the company to provide additional analysis that it needed to make decisions on issues that were key for decision making |
| **ACM2** | • After ACM2 the committee and BioMarin have agreed on several key assumptions and discussions have taken place between BioMarin and NHSE |
| **ACM3** | • The committee is only requested to evaluate cost-effectiveness for incident (new) patients.<br>↳ NHS England and the company will, independently, continue negotiations on commercial terms for prevalent (existing) patients, with the aim being to reach a deal to secure long term access for both existing and new patients following the committee meeting and informed by its evaluation. |



Abbreviations: ACM, Appraisal committee meeting; HST, Highly specialised technology; MA, Managed access; NHSE, NHS England;

# Cerliponase alfa (Brineura, BioMarin Pharmaceuticals)

| | |
|---|---|
| **Marketing authorisation** | • Cerliponase alfa is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency<br>↳ EMA approval granted on 30 May 2017 and UK marketing authorisation was granted on 1 January 2021 |
| **Mechanism of action** | • Cerliponase alfa is a recombinant form of human tripeptidyl peptidase-1 (rhTPP1), which is an enzyme replacement therapy<br>• Inadequate levels of TPP1 cause CLN2 disease, resulting in neurodegeneration, loss of neurological function and death during childhood |
| **Administration** | • Cerliponase alfa is administered to the cerebrospinal fluid by infusion via a surgically implanted intracerebroventricular infusion access device (reservoir and catheter) |
| **Price** | • List price: £20,107 per pack of cerliponase alfa (2x150 mg vials)<br>• The recommended dosage for those >2 is 300mg every other week (annual cost £522,782)<br>• Company has a confidential PAS discount in place |

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Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; EMA, European Medicines Agency; PAS, Patient access scheme TPP1, Human Tripeptidyl peptidase 1

# Clinical trial results (1/2)

CLN2 Clinical Rating Scale – ML subscale focuses on the motor and language domains

↳ Both domains are scored from 3 (normal or near-normal condition) to 0 (complete loss of function)

- A statistically significant difference was observed across all cerliponase alfa treated participants' time to first unreversed two-point decline or score of zero in ML score compared with NH controls
- A statistically significant attenuation in rate of decline was observed for cerliponase alfa treated patients across all studies compared with matched NH controls
- An increase in time to unreversed ML score of 0 was observed for all cerliponase alfa treated participants

**Table:** Clinical trial results treatment effect on adapted CLN2 ML Clinical Rating Scale

| | Study 190-201/202 | Study 190-203 | MAA FAS |
|---|---|---|---|
| **Time to first unreversed 2-point decline or score of 0 in ML score** | | | |
| **Treatment (cerliponase alfa vs NH) HR, (95% CI), p-value** | 0.06 (0.02, 0.25), <0.0001 | 0.091 (0.02, 0.39), <0.0001 | 0.126 (0.05, 0.31), <0.0001 |
| **ML score – Rate of decline (points per 48 weeks)** | | | |
| **Difference NH –cerliponase alfa treated, (95% CI), p-value** | 1.53 (0.85, 2.21), <0.0001 | 1.15 (0.80, 1.5), <0.0001 | 1.33 (0.67, 2.0), 0.0002 |
| **Time to ML score of 0** | | | |
| **Treatment (cerliponase alfa vs NH) HR, (95% CI), p-value** | 0.00 (0.00, 1.17), 0.0088 | 0.00 (0.0, NR), 0.0032 | 0.023 (0.00, 0.12), <0.0001 |

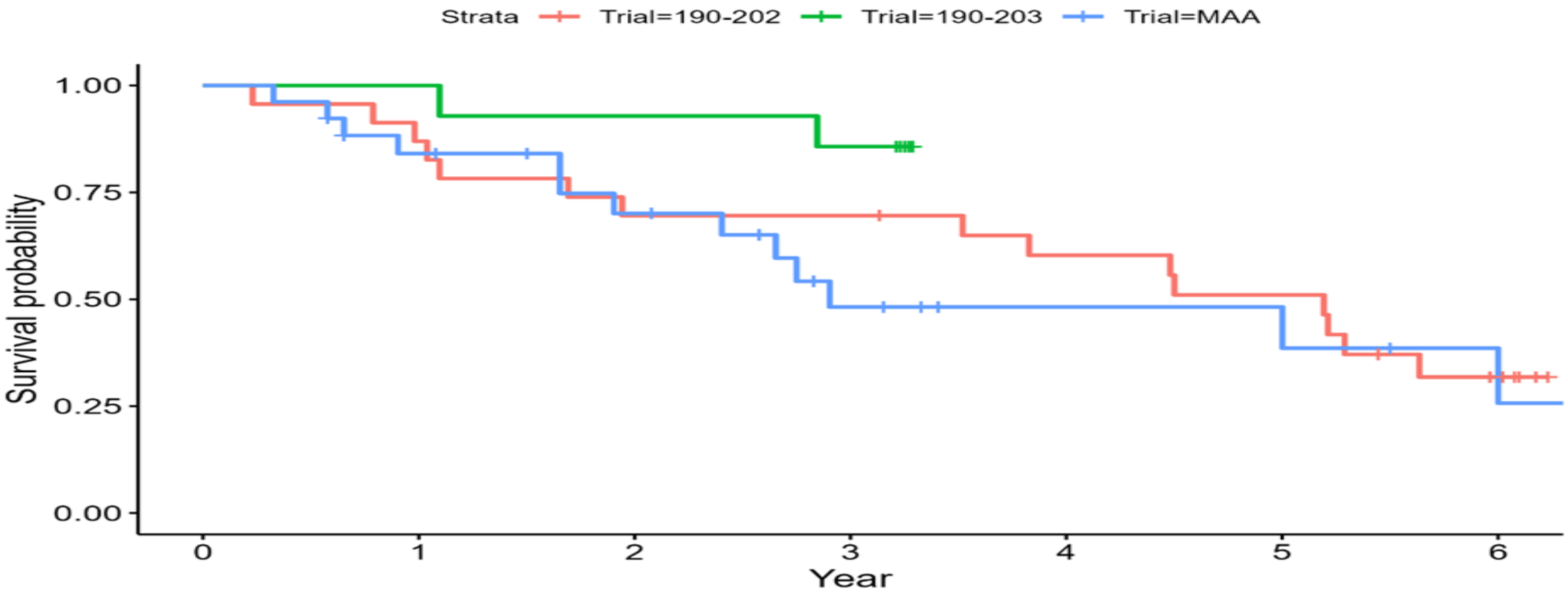
* See appendix – Time to unreversed 2-point decline or score of 0 in ML score * See appendix – Survival

* See appendix – Time to ML score of 0

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; FAS, Full analysis set; HR, Hazard ratio; ML, Motor and Language; NH, Natural history;

# Clinical trial results (2/2)

**Figure:** Time to a 2-point decline in ML score, by study




## Committee conclusion post ACM2

- The results from the studies and MAA show that cerliponase alfa is an effective treatment which provides benefits to patients, but the size of the benefit is uncertain

Abbreviations: ACM, Appraisal committee meeting; MAA, Managed access agreement; ML, Motor and Language;

# Unresolvable clinical uncertainty

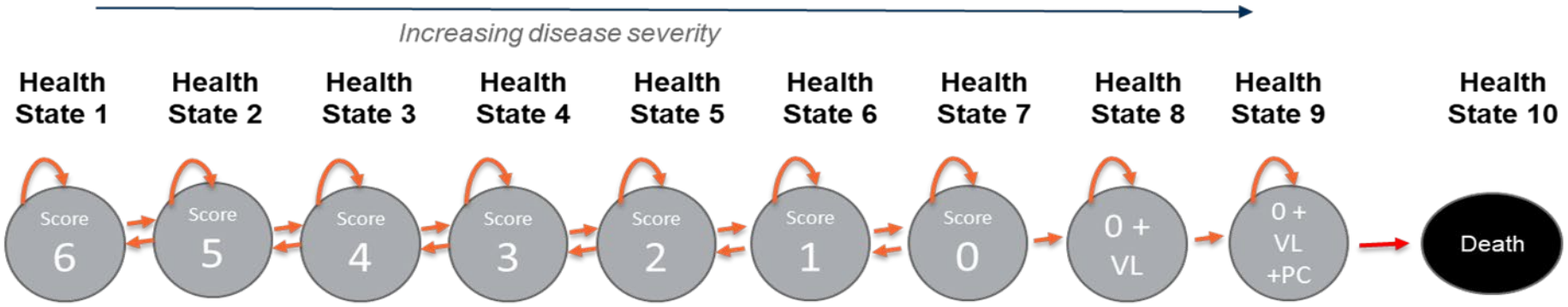
The committee concluded that there was outstanding uncertainty in the clinical effectiveness data that is unlikely to be resolved during this appraisal so it would consider the uncertainty in its decision making

| Issue | Description |
|---|---|
| **Uncertainty about trends in motor function and language** | • Disease progression after long-term use and the rate of progression in the most severe health states is unclear<br>• Rates of progression may vary across and within patients it is possible people could experience long periods of stability, or of rapid decline |
| **Uncertainty about if benefits vary with age or disease progression at treatment initiation** | • It is possible that those who start treatment younger and with limited or no disease progression experience better outcomes |
| **Uncertainty around benefits on seizure prevention** | • It is possible that cerliponase alfa may help prevent seizures or reduce their severity, but this is uncertain and so is the potential impact on QoL |
| **Uncertainty around non-neurological effects, including myoclonus and dystonia** | • Evidence on non-neurological outcomes and QoL is very limited |



Abbreviations: QoL, Quality of life

# Company's model




- Model follows a Markov cohort modelling approach
- 10 mutually exclusive health states intended to capture the disease progression of a patient from the onset of CLN2 disease through to death
- Patient transitions possible at every two-week cycle (with a half-cycle correction applied)
- Same structure as in HST12

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; HST, Highly specialised technology; PC, Palliative care; VL, Vision loss;

# Committee preferred assumptions post ACM2 (1/2)

The company are not challenging several of committee's preferred assumptions for the incident population

| Issue | Committee preferred assumption (Incident and prevalent population) |
|---|---|
| **Structural link between disease progression and other progressive symptoms** | A link between motor and language symptom progression and other progressive symptoms was acceptable<br>A treatment effect on the proportion of patients incurring the costs of progressive symptoms was plausible<br>↳ The company's estimates of the proportions in each arm was suitable for decision making |
| **Robustness of transition probability estimates in HS1-7** | The company's method to estimate transition probabilities should be used<br>Backward transitions to healthier HSs should be allowed |
| **Vision loss progression** | Cerliponase alfa has no impact on vision loss |
| **Health state utilities** | HS utilities from Gissen et al. (2021) should be used |
| **Treatment initiation** | There should be no starting rules* |

*If it was not possible to recommend cerliponase alfa for the whole population committee was open to exploring starting rules if that was a way to make cerliponase alfa available for some people, but how this could be done would need to be proposed by stakeholders

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Abbreviations: ACM, Appraisal committee meeting; HS, Health state;

# Committee preferred assumptions post ACM2 (2/2)

The company are not challenging several of committee's preferred assumptions for the incident population

| Issue | Committee preferred assumption (Incident and prevalent population) |
|---|---|
| **Treatment discontinuation** | For modelling cost-effectiveness, it should be assumed treatment stops when people reach HS7 (ML score of 0)<br>↳ But in clinical practice treatment should not be stopped just because a person has reached HS7 |
| **Other issues** | Costs for background care, ECG monitoring (in line with the SmPC) and psychiatric and behavioural support should be included<br>Neuro-disability mortality should be included in all health states. |

Abbreviations: ACM, Appraisal committee meeting; ECG, Electrocardiogram; HS, Health state; ML, Motor and Language; SmPC, Summary of product characteristics;

# Unresolved key issues after ACM2

The company has challenged some of the committee's preferred assumptions

| Issue | Committee's preferred assumptions (Incident & prevalent population) | Company's additional scenarios* |
|---|---|---|
| **Baseline distribution across health states** | Clinician estimate of the baseline distribution in 5 years' time<br>↳ HS1 (ML 6): 50%, HS2 (ML 5): 35%, HS3 (ML 4): 13%, HS4 (ML 3): 3% | Study 190-203 (<3 years)<br>↳ HS1 (ML 6): 87.5%, HS2 (ML 5): 12.5%<br>Alternative clinician best achievable estimate of the baseline distribution in 5 years' time<br>↳ HS1 (ML 6): 70%, HS2 (ML 5): 25%, HS3 (ML 4): 5% |
| **Evidence informing transition probabilities** | Pooled dataset, including data from the MAA | Study 190-203 |
| **Proportion of people who enter the model in HS1 who are initial stabilisers** | 80% | 100% |
| **Initial stabiliser risk reduction** | 50% | 75% |
| *** Aligned with clinical expert feedback from its December 2024 advisory board (received by NICE 28/03 not in time for EAG to critique) – all alternative clinician estimates for baseline distribution from ad board** | | |

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# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12)

- ❑ Recap of ACM1 and ACM2
- ✓ **Key Issues**
- ❑ Cost effectiveness

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# Key issues

| Issue | ICER impact |
|---|---|
| Baseline distribution of patients across health states | Large |
| Appropriateness of evidence source informing transition probabilities in health states 1-7 | Large |
| Proportion of people who enter the model in HS1 who are initial stabilisers | Moderate |
| Initial stabiliser risk reduction | Moderate |



Abbreviations: HS, Health state; ICER, Incremental cost-effectiveness ratio;

# Key issue: Baseline distribution across health states (1/2)

## Committee conclusion post ACM2

- Noted the clinical expert's support for the distribution that the EAG's clinical expert believed described clinical practice in 5 years' time and concluded it should be used in decision making
- Considered that the starting population was highly uncertain partly because of the impact of the pandemic

## Company response

- Baseline distribution from the Study 190-203 cohort <3 years best reflects future patients
- Clinical expert opinion is that diagnosis has improved even without newborn screening due to increased education, training, and awareness
- Proposed alternative baseline distribution described as "the best achievable scenario for patients diagnosed in 5 years' time" based on feedback received from clinical experts (advisory board - Dec 24)

## EAG comment

- Has not been able to seek further clinical expert opinion
- The proportion of people starting treatment in HS1 is a particularly influential parameter
- Using the estimated baseline distribution for clinical practice in 5-years time provided by the company increases the predicted mean time in HS1 for people that receive cerliponase alfa by:
  - ↳ 3.59 LY compared to the committee's preferred assumptions (14.45 LY and 10.86 LY, respectively)
  - ↳ 8.78 LY (attributable to baseline distribution alone) when used alongside the 3 other assumptions the company states align with the clinical expert feedback from its advisory board (Modelled mean time in HS1: 38.97 LY – as shown in later cost effectiveness results)


Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; HS, Health state; LY, Life year;

* See appendix – Baseline distribution across health

* See appendix – Baseline distribution across health

# Key issue: Baseline distribution across health states (2/2)

**Table:** Baseline distribution across health states and age scores at model entrance for different scenarios

| Health State | ML Score | Study 190-203, <3 years (N=8) *Company pref* | Study 190-203 (N=14) | MAA new patients (N=24) | Original HST12 | EAG CE *"Current clinical practice"* | EAG CE *Committee pref* | Company CE *Company pref* | CE (Patients treated at GOSH) (N=19)* | ACM1 CE |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *"Clinical practice in 5-years time"* | | | |
| **Age** | | 2 | - | - | 4 | 4.5 | 3.5 | 2.63 | *26.3%**<4 73.6% 4 - 4 yrs 11 months* | - |
| **1** | **6** | 87.5% | 50.0% | 18.2% | 50% | 15% | 50% | 70% | 10.5% | 28.5% |
| **2** | **5** | 12.5% | 7.1% | 13.6% | 50% | 45% | 35% | 25% | 10.5% | 28.5% |
| **3** | **4** | - | 21.4% | 45.5% | - | 30% | 12.5% | 5% | 57.9% | 42% |
| **4** | **3** | - | 7.1% | 13.6% | - | 10% | 2.5% | - | 10.5% | - |
| **5** | **2** | - | 7.1% | 9.1% | - | - | - | - | - | - |
| **6** | **1** | - | 7.1% | - | - | - | - | - | - | - |

*2 were non-verbal and therefore language domain was not scored but they scored 2 & 3 on motor domain ** 2 were diagnosed due to siblings

Which baseline distribution across health states best reflects that of people initiating treatment in clinical practice?

Abbreviations: ACM, Appraisal committee meeting; CE, Clinical expert; EAG, External assessment group; GOSH, Great Ormond Street Hospital; HST, Highly specialised technology; MAA, Managed access agreement; ML, Motor and Language;

# Key issue: Evidence informing transition probabilities (1/2)

## Committee conclusion post ACM2

- Pooled data, including data from the MAA, should be used for decision making
- Study 190-203 had a small sample size and limited follow up and may not reflect NHS clinical practice
  - ↳ Study 190-203 generated estimates of time spent with an ML score of 6 that appeared implausible
- COVID-19 may have meant that data from the MAA underestimates the benefits of cerliponase alfa
  - ↳ However, the 'initial stabilisers' assumption may mitigate some of the impact of delayed treatment initiation and difficulty accessing other interventions experienced in study 190-201/202 and the MAA

## Company response

- The consensus between clinical experts at its advisory board was that data from Study 190-203 best reflects current clinical practice while data from Study 190-201/202 reflects clinical practice 10 years ago

## EAG comment

- The pooled data reflects most of the evidence available given the sample size and length of follow-up
  - ↳ It may introduce bias against cerliponase alfa due to delays and interruptions to treatment
- The cohort in Study 190-203 may reflect a population younger and at an earlier point of disease progression than in NHS clinical practice
- The impact of Study 190-203 is amplified by the initial stabiliser assumptions
  - ↳ Study 190-203 more than doubles the predicted mean time in HS1 for patients that receive cerliponase alfa compared to the committee's preferred assumptions (from 10.86 LY to 22.04 LY)


Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; LY, Life year; MAA, Managed access agreement; ML, Motor and Language;

* See appendix – Evidence informing transition probabilities

# Key issue: Evidence informing transition probabilities (2/2)

## EAG comment

- Study 190-203 data is associated with considerable uncertainty due to limited sample size and follow up
  - ↳ No transitions from HS6 to HS7 were observed in Study 190-203 so the pooled data must be used to inform this transition

**Table:** Number of patients and follow-up from each study in the 'all patients' matched dataset and the natural history matched dataset

| Study | Number of patients | Length of time in study (years); mean (SD) | Length of time in study (years); median (range) |
|---|---|---|---|
| **Cerliponase alfa 'all patients' matched dataset** | 40 | 4.26 (2.00) | 3.37 (0.57, 9.00) |
| MAA "new starter" | 11 | 2.29 (1.08) | 2.55 (0.57, 3.57) |
| MAA "ex-trial" from 190-202 | 2 | 8.83 (0.24) | 8.83 (8.65, 9.00) |
| MAA "ex-trial" from 190-502 | 3 | 6.23 (0.25) | 6.09 (6.09, 6.52) |
| 190-202 | 13 | 5.70 (0.85) | 5.97 (3.11, 6.21) |
| 190-203 | 11 | 3.18 (0.13) | 3.22 (2.80, 3.23) |
| **Natural history matched dataset** | 40 | 2.67 (1.52) | 2.71 (0.50, 6.00) |

Which evidence source should be used to inform the transition probabilities?

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Abbreviations: EAG, External assessment group; HS, Health state; MAA, Managed access agreement; NH, Natural history; SD, Standard deviation;

* See appendix – Uncertainty around initial stabilisation

# Key issue: Proportion of people who enter the model in HS1 who are initial stabilisers

## Committee conclusion post ACM2

- Initial stabilisers: Remain in HS1 for 6 years. Beyond 6 years, transitions to worse health states occur at a slower rate than for those who enter the model in a worse health state and non initial stabilisers
- Assuming 80% of people who start treatment in HS1 would be initial stabilisers was more plausible and should be used for decision making (The company did not challenge this assumption at ACM2)

## Company response

- Assuming 100% of people who enter the model at HS1 would be initial stabilisers is in line with the observed data for the cohort aged <3 years in Study 190-203
- The clinical experts at its advisory board noted that:
  - ↳ Very young patients & asymptomatic siblings are more likely to remain in HS1 (ML score of 6)
  - ↳ Patients diagnosed with an ML score of 6 who are not presymptomatic, might stabilise for a certain time, but eventually experience some level of deterioration.

## EAG comment

- No new empirical evidence is available, so this remains an area of uncertainty
  - ↳ The cumulative impact of additional optimistic initial stabiliser assumptions should be noted and the clinical plausibility of modelled outcomes such as LY in HS1 (ML6) considered

What percentage of people that enter the model in HS1 should be assumed to be initial stabilisers?



Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; HS, Health state; LY, Life year; ML, Motor and Language;

* See appendix – Uncertainty around initial stabilisation

# Key issue: Initial stabiliser risk reduction

## Committee conclusion post ACM2

- At ACM1/2 risk reduction for initial stabilisers was not an area of contention between EAG and company
  - ↳ Both assumed that after 6 years initial stabilisers transition at 50% of the rate of non initial stabilisers

## Company response

- A 75% risk reduction was assumed based on feedback from clinical experts
  - ↳ At its advisory board clinical experts noted that major delays in disease progression occur under treatment with cerliponase alfa, even for patients who started treatment after onset of symptoms.

## EAG comment

- No new empirical evidence is available, so this remains an area of uncertainty
  - ↳ The cumulative impact of additional optimistic initial stabiliser assumptions should be noted and the clinical plausibility of modelled outcomes such as LY in HS1 (ML6) considered

What risk reduction should be assumed for initial stabilisers beyond 6 years?



Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; HS, Health state; LY, Life year; ML, Motor and Language;

# Equality

**Company**

- The increase in number of specialist centres across England since HST12 has improved the equality of cerliponase alfa access *(There are now 6 treatment centres)*

**Clinical expert**

- Some patients who live in remote areas do not have easy access to the treatment centres

# Innovation

**Company**

- Cerliponase alfa is a highly innovative, breakthrough technology which, has represented a step-change in the management of CLN2 disease in the UK → Before the MAA there was a significant unmet need

# Information not captured in the evaluation

**Company**

- Productivity loss for parents and other caregivers
- Out-of-pocket expenses for travel, accommodation, and home modifications
- The lifelong emotional impact of bereavement for parents, siblings, and the wider family

**Clinical expert**

- The QALY calculations do not take into account the difference in communication and perception of surroundings that are preserved in patients on treatment



Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; HST, Highly specialised technology; MAA, Managed access agreement; QALY, Quality-adjusted life year;

# Key issues

| Issue | ICER impact |
|---|---|
| Baseline distribution of patients across health states<br>↳ Which baseline distribution across health states best reflects that of people initiating treatment in clinical practice? | Large |
| Appropriateness of evidence source informing transition probabilities in health states 1-7<br>↳ Which evidence source should be used to inform the transition probabilities? | Large |
| Proportion of people who enter the model in HS1 who are initial stabilisers<br>↳ What percentage of people that enter the model in HS1 should be assumed to be initial stabilisers? | Moderate |
| Initial stabiliser risk reduction<br>↳ What risk reduction should be assumed for initial stabilisers beyond 6 years? | Moderate |



Abbreviations: HS, Health state; ICER, Incremental cost-effectiveness ratio;

# Decision modifiers: size of benefit for HST

- There needs to be compelling evidence that the treatment offers significant QALY gains
- Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator, the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained.

- QALY weightings should be calculated based only on the gain experienced by the patient
  - ↳ QALY gains experienced by others (such as carers or siblings) should be excluded

**Table:** QALY weightings for size of benefit for HSTs

| Inc QALYs gained (per patient using lifetime horizon) | Weight |
|---|---|
| ≤ 10 | 1 |
| 11 to 29 | Between 1 & 3 (using equal increments) |
| ≥ 30 | 3 |

**Example:** A QALY gain of 16.7 would result in a weighting of 1.67, leading to a threshold of £167,000

**Table:** QALY weightings and thresholds for size of benefit for HSTs

| Number of additional QALYs (X) | Weight | Threshold |
|---|---|---|
| ≤ 10 | 1 | £100, 000 |
| 10 < X< 30 | W = X/10 | W * £100, 000 |
| ≥ 30 | 3 | £300, 000 |

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Abbreviations: Inc, Incremental; QALY, Quality-adjusted life year;

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12)

- ❑ Recap of ACM1 and ACM2
- ❑ Key issues
- ✓ **Cost effectiveness**

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# Cost-effectiveness – Individual scenarios (1/2)

- All ICERs are calculated using the confidential PAS discount for cerliponase alfa
- At the current discount the ICERs for all scenarios are substantially above what NICE considers an acceptable use of NHS resources
- Modelled mean undiscounted LY in HS1 (ML6) is provided for each scenario to explore the cumulative impact of assumptions and check for clinical plausibility

**Table:** Cost-effectiveness results committee preferred assumptions at ACM2 and individual scenarios

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities) | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Committee preferred assumptions at ACM2** | | | | | | | | |
| SoC | [redacted] | -0.71 | | | | | | 0.29 |
| Cerliponase alfa | [redacted] | 8.01 | [redacted] | 8.72 | [redacted] | [redacted] | [redacted] | 10.86 |
| **Scenario 1: Baseline distribution taken from Study 190-203 (<3 years)** | | | | | | | | |
| SoC | [redacted] | -0.42 | | | | | | 0.51 |
| Cerliponase alfa | [redacted] | 11.71 | [redacted] | 12.13 | [redacted] | [redacted] | [redacted] | 17.51 |
| **Scenario 2: Transition probabilities from Study 190-203** | | | | | | | | |
| SoC | [redacted] | -0.61 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 11.17 | [redacted] | 11.77 | [redacted] | [redacted] | [redacted] | 22.04 |

*Undiscounted

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cost-effectiveness – Individual scenarios (2/2)

**Table:** Cost-effectiveness results individual scenarios

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Scenario 3: 100% of people who enter the model at health state 1 would be initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.71 | | | | | | 0.29 |
| Cerliponase alfa | [redacted] | 8.69 | [redacted] | 9.41 | [redacted] | [redacted] | [redacted] | 12.25 |
| **Scenario 4: 75% risk reduction for initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.71 | | | | | | 0.29 |
| Cerliponase alfa | [redacted] | 9.33 | [redacted] | 10.04 | [redacted] | [redacted] | [redacted] | 15.76 |
| **Scenario 5: Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.55 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 10.02 | [redacted] | 10.57 | [redacted] | [redacted] | [redacted] | 14.45 |

*Undiscounted

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cost-effectiveness – Combination of Individual scenarios (1/6)

**Table:** Cost-effectiveness results combination of individual scenarios (Table 1)

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Scenario 1 and 2: Baseline distribution taken from Study 190-203 (<3 years) & Transition probabilities from Study 190-203** | | | | | | | | |
| SoC | [redacted] | -0.22 | | | | | | 0.72 |
| Cerliponase alfa | [redacted] | 15.03 | [redacted] | 15.25 | [redacted] | [redacted] | [redacted] | 31.78 |
| **Scenario 1 and 3: Baseline distribution taken from Study 190-203 (<3 years) & 100% of people who enter the model at health state 1 would be initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.42 | | | | | | 0.51 |
| Cerliponase alfa | [redacted] | 12.91 | [redacted] | 13.33 | [redacted] | [redacted] | [redacted] | 19.95 |
| **Scenario 1 and 4: Baseline distribution taken from Study 190-203 (<3 years) & 75% risk reduction for initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.42 | | | | | | 0.51 |
| Cerliponase alfa | [redacted] | 14.04 | [redacted] | 14.46 | [redacted] | [redacted] | [redacted] | 26.19 |

*Undiscounted

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cost-effectiveness – Combination of Individual scenarios (2/6)

**Table:** Cost-effectiveness results combination of individual scenarios (Table 2)

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Scenario 2 and 3: Transition probabilities from Study 190-203 & 100% of people who enter the model at health state 1 would be initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.61 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 11.75 | [redacted] | 12.36 | [redacted] | [redacted] | [redacted] | 23.87 |
| **Scenario 2 and 4: Transition probabilities from Study 190-203 & 75% risk reduction for initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.61 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 12.13 | [redacted] | 12.74 | [redacted] | [redacted] | [redacted] | 27.09 |
| **Scenario 2 and 5: Transition probabilities from Study 190-203 & Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.39 | | | | | | 0.58 |
| Cerliponase alfa | [redacted] | 13.32 | [redacted] | 13.71 | [redacted] | [redacted] | [redacted] | 27.40 |

*Undiscounted

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cost-effectiveness – Combination of Individual scenarios (3/6)

**Table:** Cost-effectiveness results combination of individual scenarios (Table 3)

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Scenario 3 and 4: 100% of people who enter the model at health state 1 would be initial stabilisers & 75% risk reduction for initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.71 | | | | | | 0.29 |
| Cerliponase alfa | [redacted] | 10.34 | [redacted] | 11.06 | [redacted] | [redacted] | [redacted] | 18.37 |
| **Scenario 3 and 5: 100% of people who enter the model at health state 1 would be initial stabilisers & Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.55 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 10.98 | [redacted] | 11.53 | [redacted] | [redacted] | [redacted] | 16.40 |
| **Scenarios 4 and 5: 75% risk reduction for initial stabilisers & Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.55 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 11.88 | [redacted] | 12.43 | [redacted] | [redacted] | [redacted] | 21.36 |

*Undiscounted

NICE Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cost-effectiveness – Combination of Individual scenarios (4/6)

**Table:** Cost-effectiveness results combination of individual scenarios (Table 4)

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Scenario 1, 2 and 3: Baseline distribution taken from Study 190-203 (<3 years) & Transition probabilities from Study 190-203 & 100% of people who enter the model at health state 1 would be initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.22 | | | | | | 0.72 |
| Cerliponase alfa | [redacted] | 16.06 | [redacted] | 16.28 | [redacted] | [redacted] | [redacted] | 35.03 |
| **Scenarios 1, 2 and 4: Baseline distribution taken from Study 190-203 (<3 years) & Transition probabilities from Study 190-203 & 75% risk reduction for initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.22 | | | | | | 0.72 |
| Cerliponase alfa | [redacted] | 16.74 | [redacted] | 16.96 | [redacted] | [redacted] | [redacted] | 40.85 |
| **Scenarios 1, 2, 3, and 4: Baseline distribution taken from Study 190-203 (<3 years) & Transition probabilities from Study 190-203 & 100% of people who enter the model at health state 1 would be initial stabilisers & 75% risk reduction for initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.22 | | | | | | 0.72 |
| Cerliponase alfa | [redacted] | 18.19 | [redacted] | 18.41 | [redacted] | [redacted] | [redacted] | 46.37 |

*Undiscounted

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cost-effectiveness – Combination of Individual scenarios (5/6)

**Table:** Cost-effectiveness results combination of individual scenarios (Table 5)

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Scenarios 2, 3 and 4: Transition probabilities from Study 190-203 & 100% of people who enter the model at health state 1 would be initial stabilisers & 75% risk reduction for initial stabilisers** | | | | | | | | |
| SoC | [redacted] | -0.61 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 12.95 | [redacted] | 13.56 | [redacted] | [redacted] | [redacted] | 30.19 |
| **Scenarios 2, 3 and 5: Transition probabilities from Study 190-203 & 100% of people who enter the model at health state 1 would be initial stabilisers & Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.39 | | | | | | 0.58 |
| Cerliponase alfa | [redacted] | 14.14 | [redacted] | 14.53 | [redacted] | [redacted] | [redacted] | 29.98 |
| **Scenarios 2, 4 and 5: Transition probabilities from Study 190-203 & 75% risk reduction for initial stabilisers & Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.39 | | | | | | 0.58 |
| Cerliponase alfa | [redacted] | 14.68 | [redacted] | 15.07 | [redacted] | [redacted] | [redacted] | 34.58 |

*Undiscounted

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cost-effectiveness – Combination of Individual scenarios (6/6)

**Table:** Cost-effectiveness results combination of individual scenarios (Table 6)

| Technology | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£/QALY) | CoE threshold (Carer / sibling disutilities | | LY in HS1 (ML 6)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Excluded | Included | |
| **Scenarios 3, 4 and 5: 100% of people who enter the model at health state 1 would be initial stabilisers & 75% risk reduction for initial stabilisers & Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.55 | | | | | | 0.41 |
| Cerliponase alfa | [redacted] | 13.30 | [redacted] | 13.85 | [redacted] | [redacted] | [redacted] | 25.03 |
| **Scenarios 2, 3, 4, and 5: Transition probabilities from Study 190-203 & 100% of people who enter the model at health state 1 would be initial stabilisers & 75% risk reduction for initial stabilisers & Baseline distribution from company clinical expert opinion in 5 years (ML 6: 70%, ML 5: 25%, ML 4: 5%)** | | | | | | | | |
| SoC | [redacted] | -0.39 | | | | | | 0.58 |
| Cerliponase alfa | [redacted] | 15.84 | [redacted] | 16.23 | [redacted] | [redacted] | [redacted] | 38.97 |

*Undiscounted

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; LY, Life years; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12)

# Supplementary appendix

NICE National Institute for Health and Care Excellence

# Background on neuronal ceroid lipofuscinosis type 2 (CLN2)

CLN2 is a rare rapidly progressive and devastating condition that affects infants and children

**Causes**

- Inherited autosomal recessive condition caused by pathogenic variants/mutations in the TPP1/CLN2 gene
- Leads to deficient activity of lysosomal enzyme (TPP1)
- A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells
- Accumulation of proteins and lipids prevents the cells from functioning as they should

**Epidemiology**

- Company: ~40 people with CLN2 in England, EAG clinical advice: 50 in the UK
- Estimated that around 6 children are diagnosed with CLN2 in the UK each year

**Diagnosis and classification**

- Based on laboratory testing following clinical suspicion → Demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) and the identification of pathogenic variants in both alleles of the *TPP1/CLN2* gene

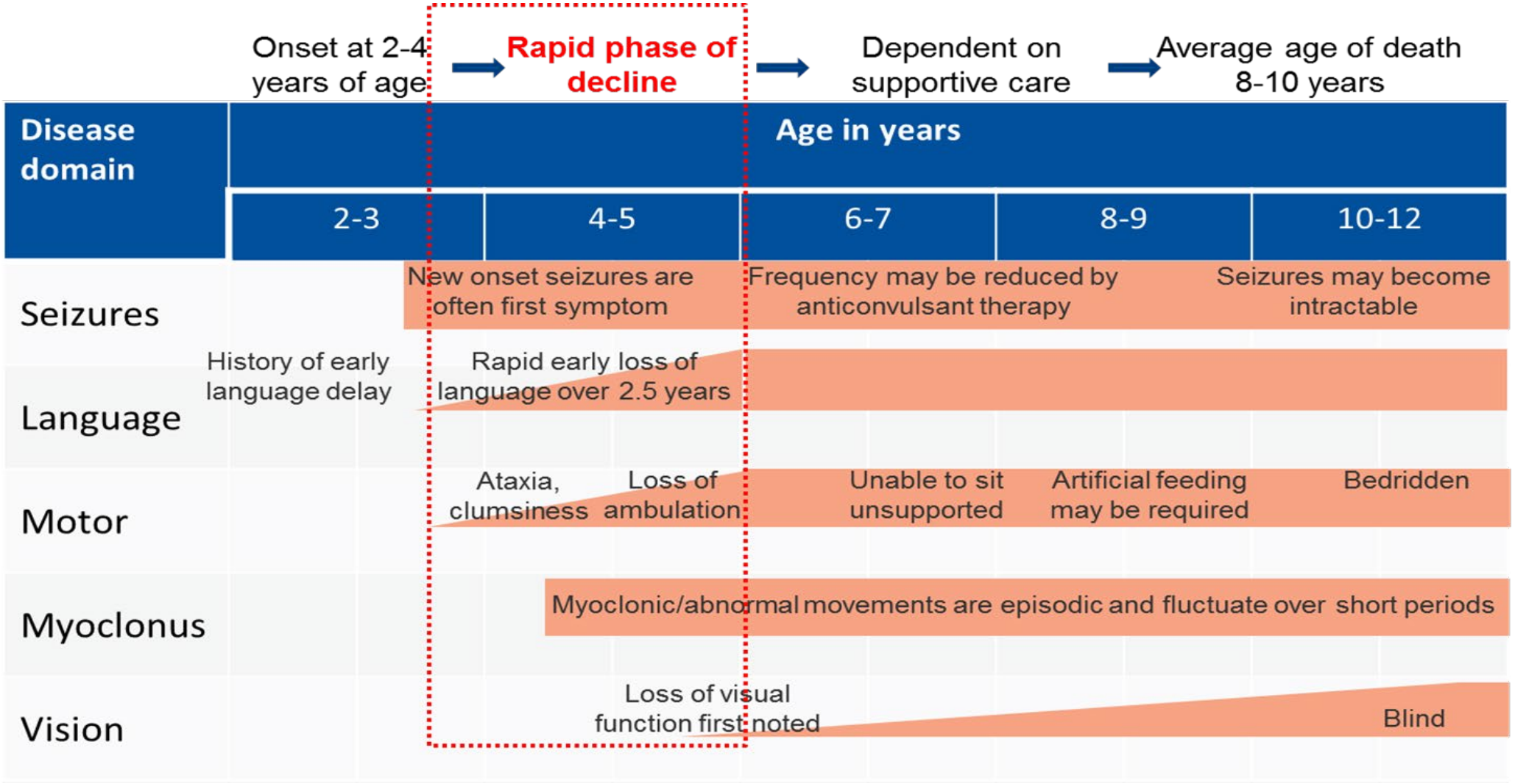
**Symptoms and prognosis**

- Following presentation in late infancy CLN2 progresses rapidly and predictably
- CLN2 is characterised clinically by a decline in mental and other capacities, seizures and usually sight loss
- Life expectancy is around 6 to 12 years



Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; TPP1, Human Tripeptidyl peptidase 1;

# Course of CLN2 disease




The rapid progression of the disease means that by the age of 6, most children will be completely dependent on families and carers for all of their daily needs

# Patient perspectives (1)

## CLN2 is a cruel and devastating neurodegenerative disorder

**Submissions from Batten Disease Family Association (BDFA)**

- CLN2 has a negative impact on every aspects of a child's development such as self-care, ability to play games with friends, participate in family activities and their schooling
- Caring for children with CLN2 has a profound impact on parents and unaffected siblings and it is difficult to retain normal family activities

*"Children receiving regular treatment have a much slower deterioration, especially with mobility and muscle strength. The treatment is invaluable for these children and allows them to maintain independence and a better quality of life for longer."*

*"Cerliponase alfa … is a groundbreaking and life transforming treatment that directly addresses the cause of the disease"*

- Unmet need
  - ↳ Apart from cerliponase alfa the only treatment options are symptomatic treatments that do not address the underlying cause of the disease
  - ↳ There is still a long and unacceptable delay to diagnosis that results in children receiving treatment when their disease has already progressed and potentially resulting in a false perception about the lack of treatment affect

*"Many parents could not mention anything negative about a treatment which they see as bringing benefit to their child's increased longevity and quality of life"*

- Results from national surveys with families of children diagnosed with CLN2 and with educational workers have been shared with committee alongside videos showing the positive impact cerliponase alfa has had

Abbreviations: BDFA, Batten Disease Family Association; CLN2, Neuronal ceroid lipofuscinosis type 2;

# Patient perspectives (2)

## Submissions from 3 patient experts

*"Living with the degenerative nature of the condition is the hardest part because you know you are powerless to stop it and you will be forced to watch helplessly on as your child loses the abilities you watched them accomplish with so much joy and excitement."*

- Families are shocked to learn that a child who was born healthy has a rapidly progressive disease
- Parents of children with CLN2 can experience anticipatory grief and extreme isolation
- CLN2 impacts every aspect of family life and can have a substantial financial impact
- Some families have more than one child with CLN2

*"Cerliponase alfa … is saving our youngest daughter's abilities and saving her life. She is gaining skills and building the most wonderful relationships…She is doing things we never got to see our older daughter do"*

- Cerliponase alfa allows children to attend school, travel (including by plane) and create memories
- Parents knowing that their child is receiving an effective treatment gives them hope for a longer healthier life for their child

- Early diagnosis and access to treatment is extremely important because delays to diagnosis mean that children lose skills which they will never get back
- When treatment is available in local hospitals it alleviates the burden of travel and feels more comfortable
- Families face a 'postcode lottery' of care depending on where they live and often have to fight to get the support they are entitled to

*" [Cerliponase alfa] has given our children and us as a family the gift of time, it has improved quality of life massively, eased the amount of pain experienced and reduced seizures. "*

# Clinical perspectives

## Cerliponase alfa has transformed the way CLN2 is perceived

**Submissions from 2 clinical experts**

- Without cerliponase alfa the only alternative treatment is supportive care
- When patients receive cerliponase alfa they do not follow the natural history of the condition and remain in much better health for many years
  - ↳ CLN2 is now considered a treatable condition
- Slowing progression means that the parents and the family have longer time to enjoy life with their children
- Most patients benefit from cerliponase alfa but the best outcomes are observed in those that are pre-symptomatic or have had an early diagnosis.
  - ↳ Unless treatment can start pre-symptomatically patients will require clinical follow up and management of symptoms
- Patients treated with cerliponase alfa use fewer healthcare resources compared to the untreated cohort

*"The patients treated with cerliponase alfa will live longer and will remain in much better state compared with the patients who are not treated"*

**NICE**



Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2;

# Decision problem (1/3)

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Population** | People with CLN2 | As per scope | - |
| **Intervention** | Cerliponase alfa | As per scope | - |
| **Subgroup** | If the evidence allows, the following subgroup should be considered:<br>Stage of progression of CLN2 | Scenario analyses are presented in which alternative baseline health state distributions are considered. | Subgroup analyses based on age and ML score at treatment initiation may have been helpful but would have limited statistical power |
| **Comparator** | Established clinical management without cerliponase alfa (including managing the symptoms and complications associated with CLN2) | As per scope | - |
| **Outcomes** | Symptoms of CLN2 including visual function, seizures, myoclonus, dystonia, spasming, pain, and feeding<br>Disease progression<br>• CLN2 Clinical Rating Scale (reported as 4-domain scale and combined score of the motor and language domains)<br>• Weill Cornell LINCL Scale (4-domain scale)<br>• Hamburg scale | Majority of analyses based on disease progression, using CLN2 Clinical Rating Scale<br>Focus on the CLN2 Clinical Rating Scale, including a 2-domain (motor and language) subscale called the ML scale. | The company focused on the ML scale with little reporting of vision and seizure components (although those data were later supplied at the EAG's request). |

# Decision problem (2/3)

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Outcomes continued** | • Neurological development which may be informed by measures specified in the MAA for HST12 including Bayley Scales of Infant Development III, WPPSI-IV, Vineland Adaptive Behaviour Scale, and WISC-V<br>• Need for medical care (including hospitalisation, emergency care and primary and secondary care appointments, and concomitant medication)<br>• Mortality<br>• Adverse effects of treatment (including immune response and effects and complications related to treatment administration)<br>• HRQoL (for patients and carers and including impact on families such as social and mental health and impact on siblings). This may be informed by QoL measures including PedsQL, EQ-5D, and CLN2-QL. Compliance/adherence to treatment | Data on spasming (i.e. muscular contraction only), pain, and feeding were not directly reported, they were collected via other outcomes; spasming is a sign of myoclonus/dystonia, feeding function was assessed as part of the Weill Cornell LINCL Scale, and pain was covered by the PedsQL and CLN2 QL questionnaires.<br><br>The only need for medical care variable collected was seizures that require doctor/hospital visits. No other need for medical care information was collected as part of the clinical evidence.<br><br>No other differences from final scope. | • Acknowledges that not all the outcomes were collected in the included studies.<br>• Company's approach of supplying data from other sources is reasonable.<br>• Notes the lack of evidence on neurological development and need for medical care. |

# Decision problem (3/3)

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Economic analysis** | The use of cerliponase alfa is conditional on the presence of CLN2. The economic modelling should include the costs associated with diagnostic testing for CLN2 in people with CLN2 disease who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. | Diagnostic testing costs have not been included as it is expected that all patients with CLN2 disease would be diagnosed, irrespective of the availability of cerliponase alfa. | Company's economic analysis is mostly in line with the decision problem.<br><br>The EAG considers that the exclusion of diagnostic testing costs is appropriate and is satisfied by the company's scenario analysis on this parameter that this is not an issue likely to impact on the estimates of cost-effectiveness. |

# Key clinical trials*

**Table:** Summary characteristic of the studies

| | 190-201 (n=24) | 190-202 (n=24) | 190-203 (n=14) | MAA (n=35) | 190-901 (n=42) |
|---|---|---|---|---|---|
| **Design** | Phase 1/2 Single-arm open label | Phase 2 Single-arm open label extension | Phase 2 Single-arm open label study | Data collection agreement | Natural history study |
| **Population** | Aged 3 to 16 years | Those who completed Study 190-201 | Primarily <3 years of age and required enrolment of at least five participants <2 years of age | People who started treatment in a study or the EAP (n=11)<br>People who have never received treatment and start treatment at ≥ 3 years of age (n=24) | People with untreated CLN2 |
| **Data cuts / Follow up** | December 2020 - 48 weeks | December 2020 - 240 weeks | April 2022 –169 weeks | September 2023 – 209 weeks | NR |
| **Intervention** | Cerliponase alfa | | | | N/A |
| **Primary outcome** | CLN2 Clinical Rating Scale – ML subscale. | | | | |
| **Secondary outcomes** | CLN2 clinical rating scale total score and individual domains: motor, language, vision, seizure | | | | |
| **Locations** | US, Germany, Italy, UK | | | UK | Germany, Italy |

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; EAP, Early access program; ML, Motor and Language; N/A, Not applicable; NR, Not reported;

# Comparison of baseline characteristics (1/2)

**Table:** Baseline characteristics for NH and 190-201/202 (1:1 matched patients)

| | NH (n=17) | 190-201/202 (n=17) |
|---|---|---|
| **Age at enrolment (years)** | | |
| Mean (SD) | 4.6 (0.72) | 4.6 (0.74) |
| Median | 4.3 | 4.4 |
| Min, Max | 3.4, 6.3 | 3.3, 6.3 |
| **Sex** | | |
| Female | 7 (41%) | 11 (65%) |
| Male | 10 (59%) | 6 (35%) |
| **Baseline ML score** | | |
| 6 | 2 (12%) | 2 (12%) |
| 5 | 1 (6%) | 1 (6%) |
| 4 | 4 (24%) | 4 (24%) |
| 3 | 7 (41%) | 7 (41%) |
| 2 | 2 (12%) | 2 (12%) |
| 1 | 1 (6%) | 1 (6%) |

**Table:** Baseline characteristics for NH and 190-203 (3:1 matched patients)

| | NH (n=29) | 190-203 (n=12) |
|---|---|---|
| **Age at enrolment (years)** | | |
| Mean (SD) | 2.7 (1.09) | 2.7 (1.12) |
| Median | 2.5 | 2.5 |
| Min, Max | 1.1, 4.5 | 1.1, 4.5 |
| **Sex** | | |
| Female | 15.3 (52.8%) | 8 (66.7%) |
| Male | 13.7 (47.2%) | 4 (33.3%) |
| **CLN2 ML score** | | |
| Mean (SD) | 5.0 (1.38) | 5.0 (1.41) |
| Median (min, max) | 6.0 (2.0, 6.0) | 6.0 (2.0, 6.0) |
| **Age at disease onset (years)** | | |
| n | 11 | 5 |
| Mean (SD) | 2.6 (0.82) | 2.1 (0.82) |
| Median (min, max) | 3.0 (1.3, 3.7) | 2.0 (1.5, 3.5) |

Link to – Key clinical trials

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; ML, Motor and Language; NH, Natural history; SD, Standard deviation;

# Comparison of baseline characteristics (2/2)

**Table:** Baseline characteristics for NH and MAA (1:1 matched patients)

| | NH and MAA FAS matched patients | | NH and MAA new starter matched patients | |
|---|---|---|---|---|
| | NH (n=26) | MAA FAS (n=26) | NH (n=17) | MAA new starters (n=17) |
| **Age at baseline (years)** | | | | |
| **n** | 26 | 26 | 17 | 17 |
| **Mean (SD)** | 4.35 (1.11) | 4.37 (1.07) | 4.53 (1.18) | 4.56 (1.10) |
| **Median (Min, Max)** | 4.25 (1.75,8.75) | 4.33 (1.72, 8.5) | 4.25 (3.33, 8.75) | 4.33 (3.5, 8.5) |
| **Sex, n (%)** | | | | |
| **Female** | 13 (50%) | 6 (23%) | 9 (53%) | 0 |
| **Unknown** | 0 | 17 (65%) | 0 | 17 (100%) |
| **Baseline ML score** | | | | |
| **Mean (SD)** | 4 (1.26) | 4 (1.26) | 4.12 (1.11) | 4.12 (1.11) |
| **Baseline ML score, n (%)** | | | | |
| **1** | 1 (3.85%) | 1 (3.85) | 0 | 0 |
| **2** | 3 (11.54%) | 3 (11.54%) | 2 (11.76%) | 2 (11.76%) |
| **3** | 2 (7.69%) | 2 (7.69%) | 1 (5.88%) | 1 (5.88%) |
| **4** | 12 (46.15%) | 12 (46.15%) | 9 (52.94%) | 9 (52.94%) |
| **5** | 5 (19.23%) | 5 (19.23%) | 3 (17.64%) | 3 (17.64%) |
| **6** | 3 (11.54%) | 3 (11.54%) | 2 (11.76%) | 2 (11.76%) |
| **Age at disease onset, months** | | | | |
| **n** | 26 | 4 | 17 | NR |
| **Mean (SD)** | 36.19 (7.22) | 34 (2.16) | 37.12 (5.43) | NR |

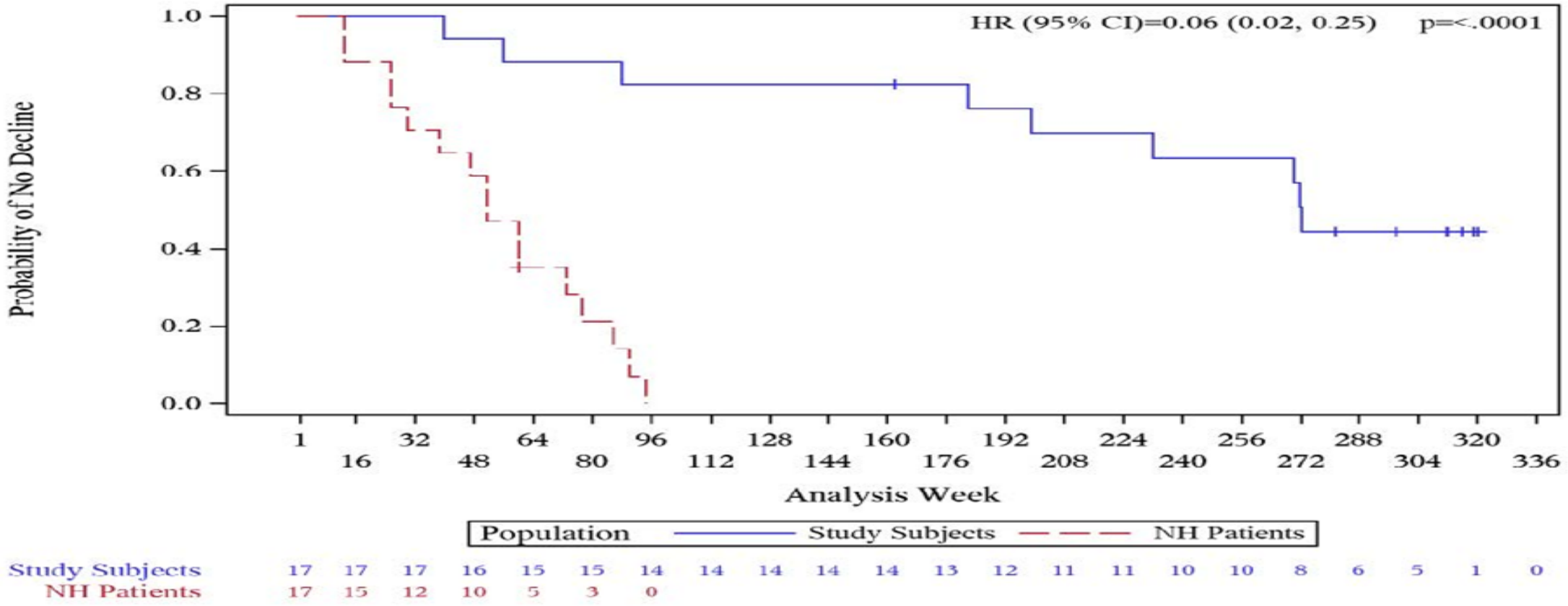
Link to – Key clinical trials



Abbreviations: FAS, Full analysis set; MAA, Managed access agreement; ML, Motor and Language; NH, Natural history; SD, Standard deviation;

# Time to unreversed 2-point decline or score of 0 in ML score – 190-201/202

**Figure:** Time to first unreversed 2-point decline or score of 0 in ML score (1:1 matched NH and 190-201/202 population



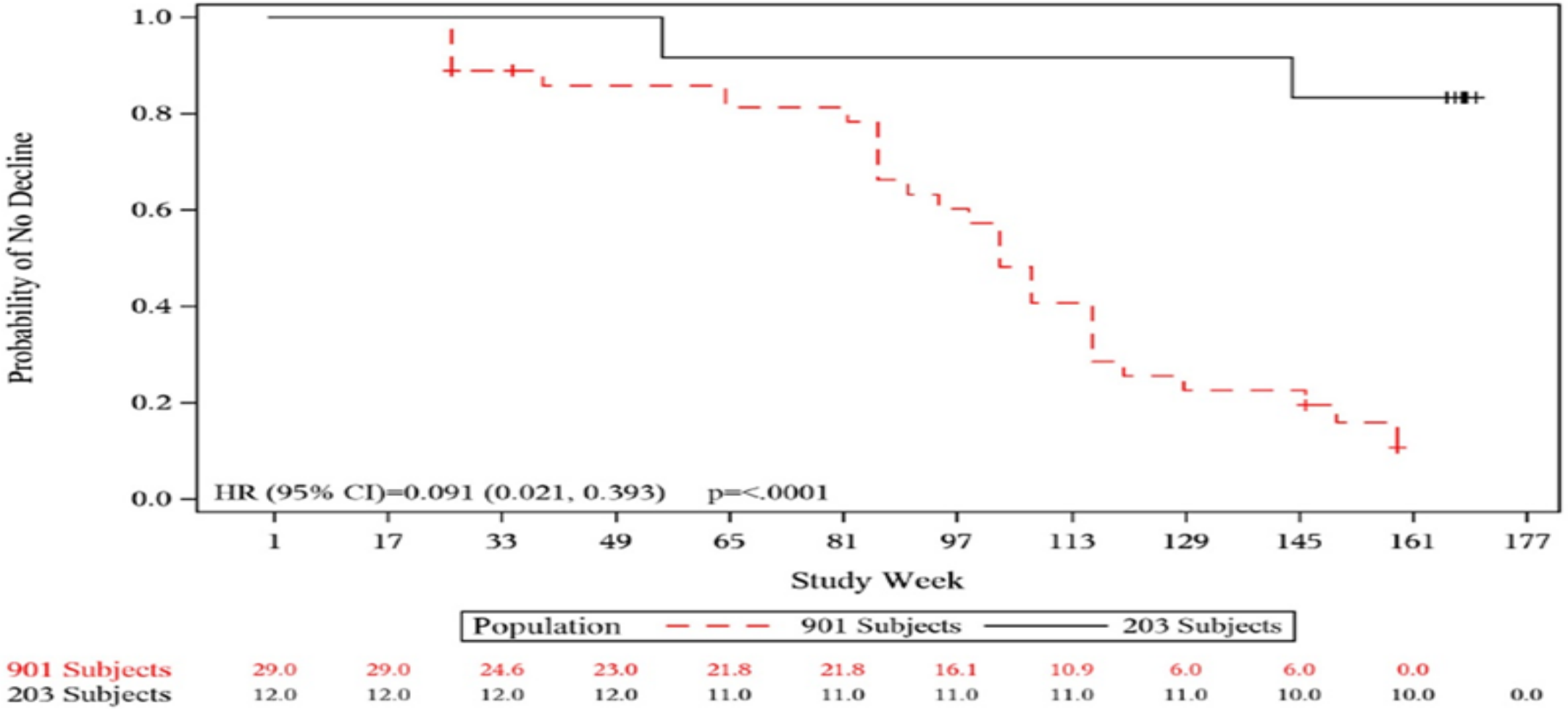

Link to – Clinical trials results

NICE

Abbreviations: ML, Motor and Language; NH, Natural history;

# Time to unreversed 2-point decline or score of 0 in ML score – 190-203

**Figure:** Time to first unreversed 2-point decline or score of 0 in ML (3:1 matched NH and 190-203 population)



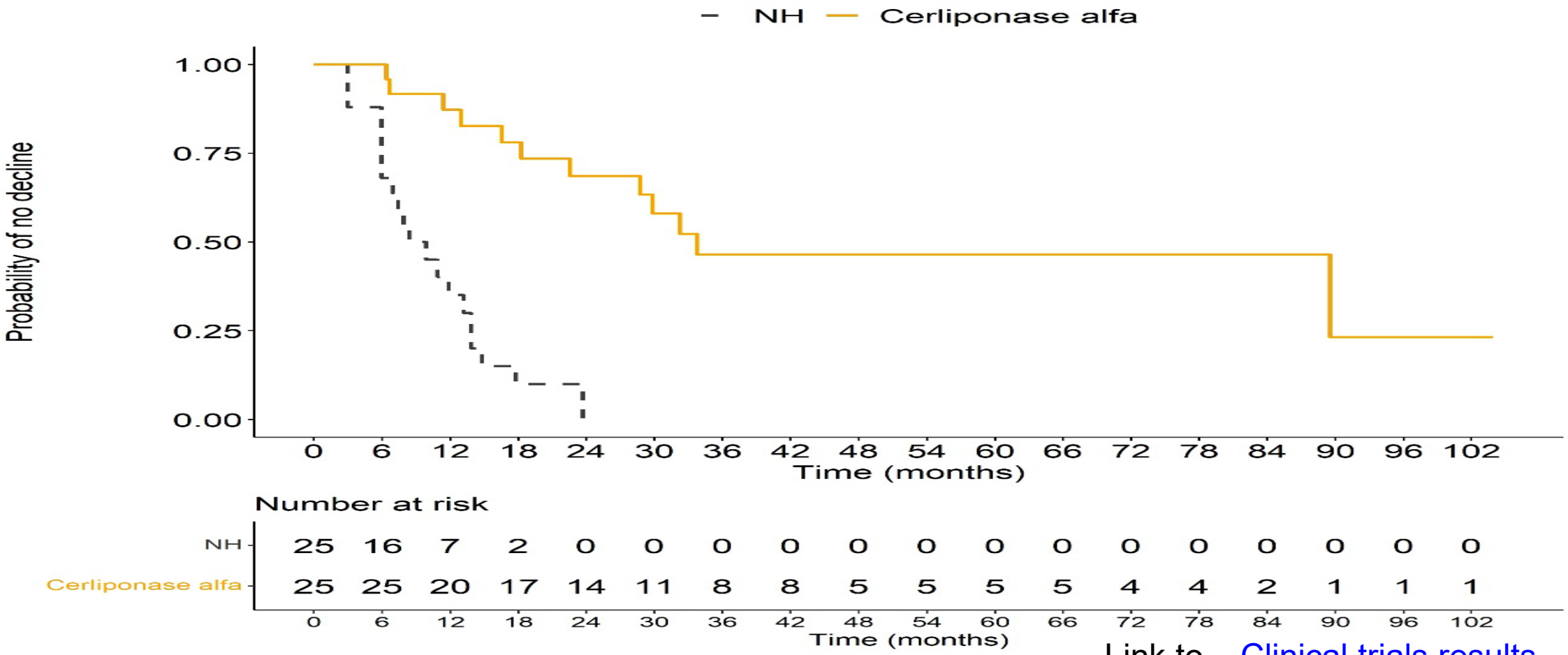

NICE

Abbreviations: ML, Motor and Language; NH, Natural history;

Link to – Clinical trials results

# Time to unreversed 2-point decline or score of 0 in ML score – MAA cohort

**Figure:** Time to first unreversed 2-point decline or score of 0 in ML score (1:1 matched NH and MAA FAS)

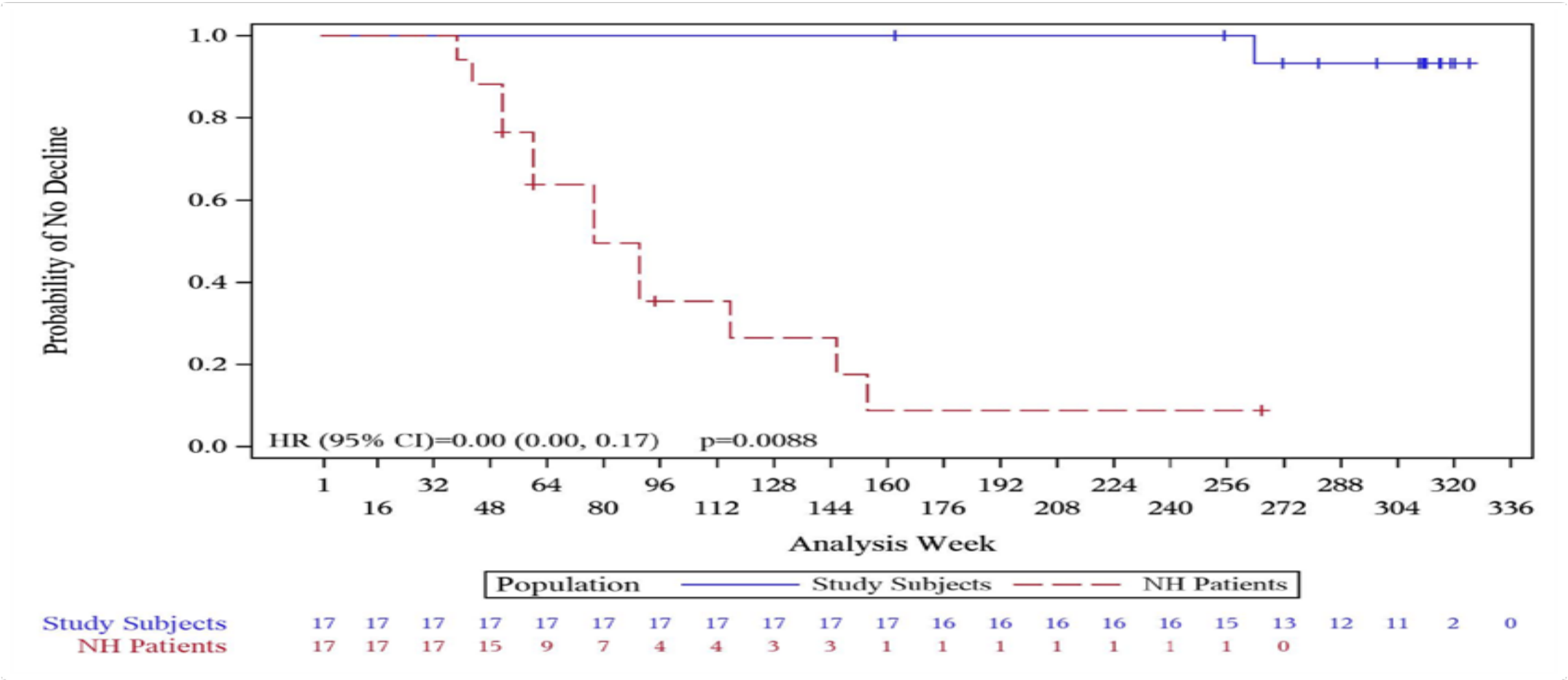



Link to – Clinical trials results

Abbreviations: FAS, Full analysis set; MAA, Managed access agreement; ML, Motor and Language; NH, Natural history;

# Time to ML score of 0 - 190-201/202

**Figure:** Time to score of 0 in ML score (1:1 matched NH and 190-201/202 population)



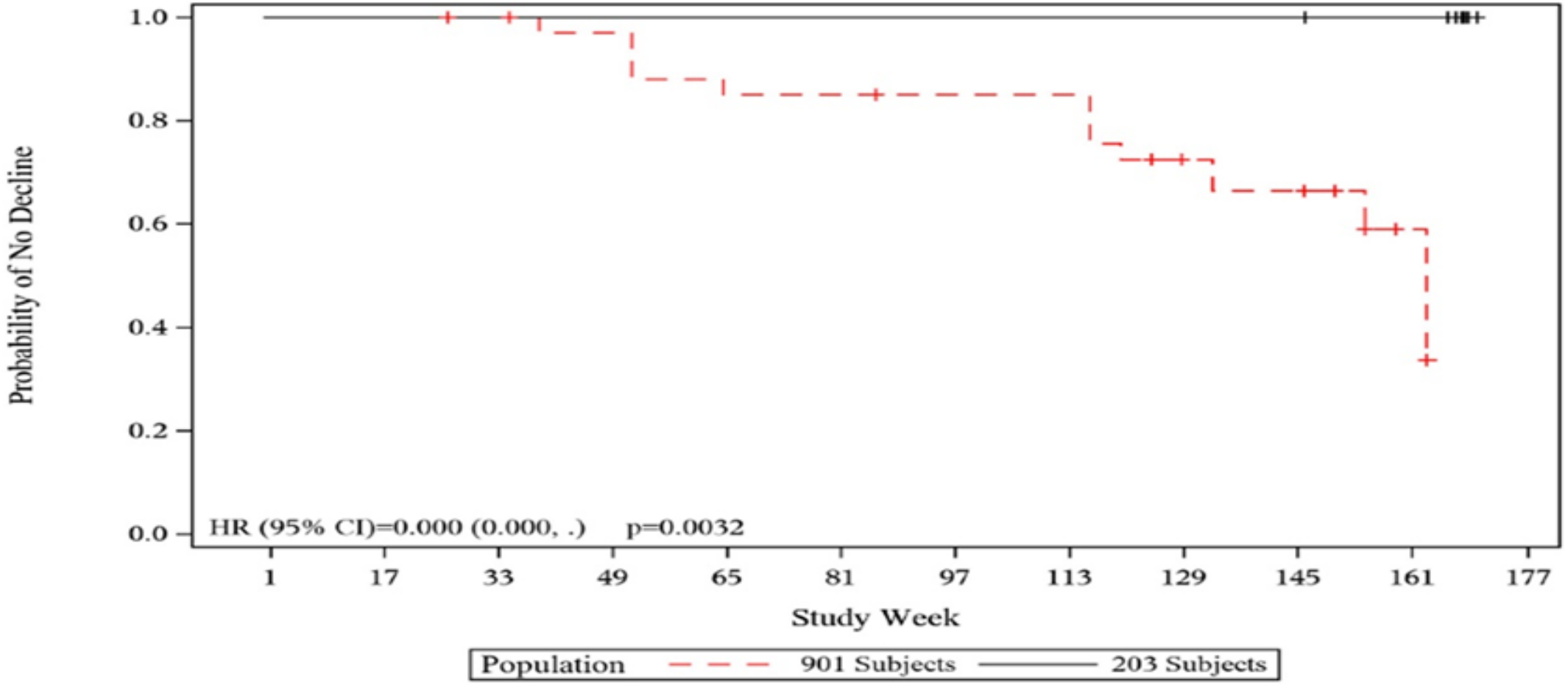

Link to – Clinical trials results

NICE

Abbreviations: ML, Motor and Language; NH, Natural history;

# Time to ML score of 0 - 190-203

**Figure:** Time to score of 0 in ML score (3:1 matched NH and 190-203 population)

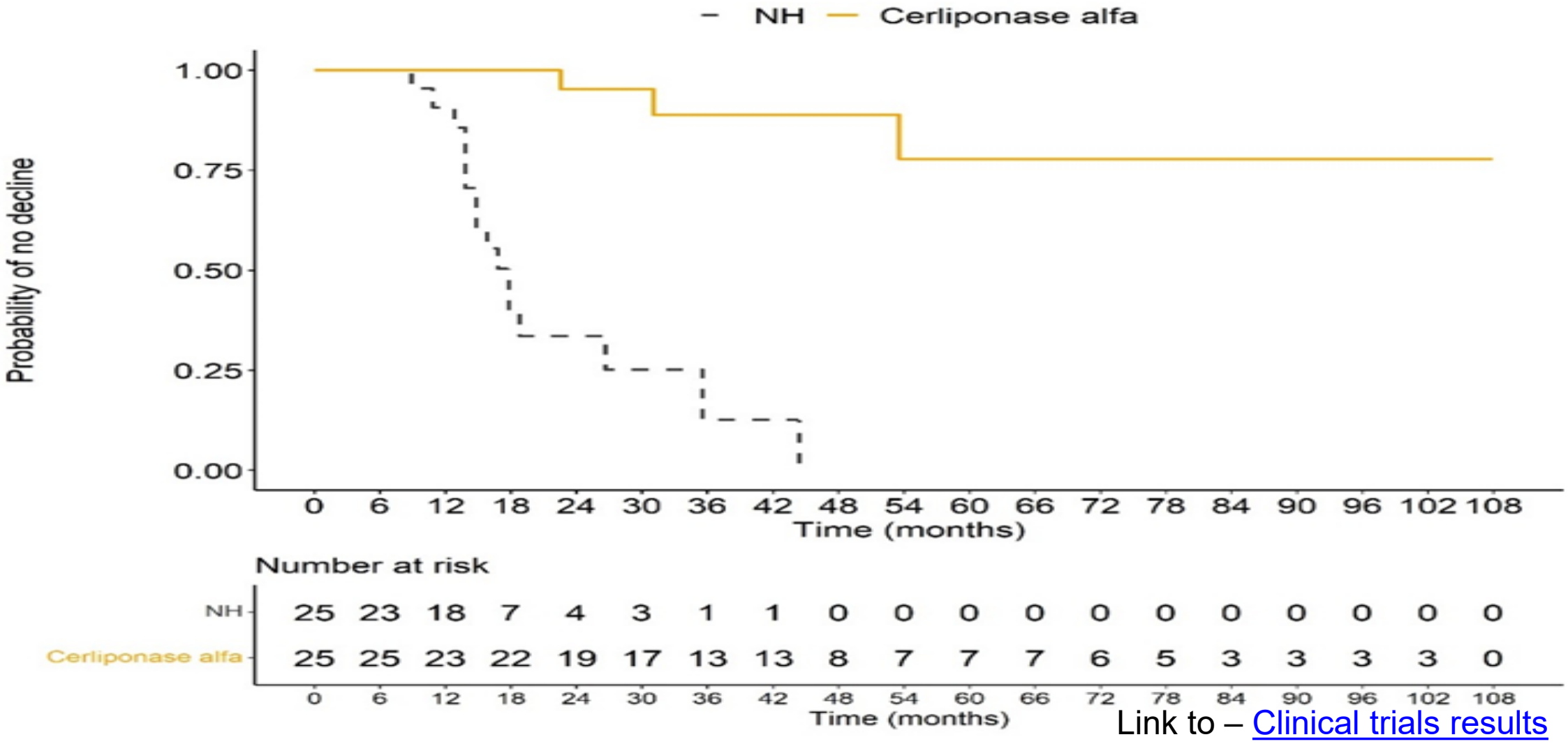



Link to – Clinical trials results

Abbreviations: ML, Motor and Language; NH, Natural history;

# Time to ML score of 0 – MAA cohort

**Figure:** Time to score of 0 in ML score (1:1 matched NH and MAA FAS)

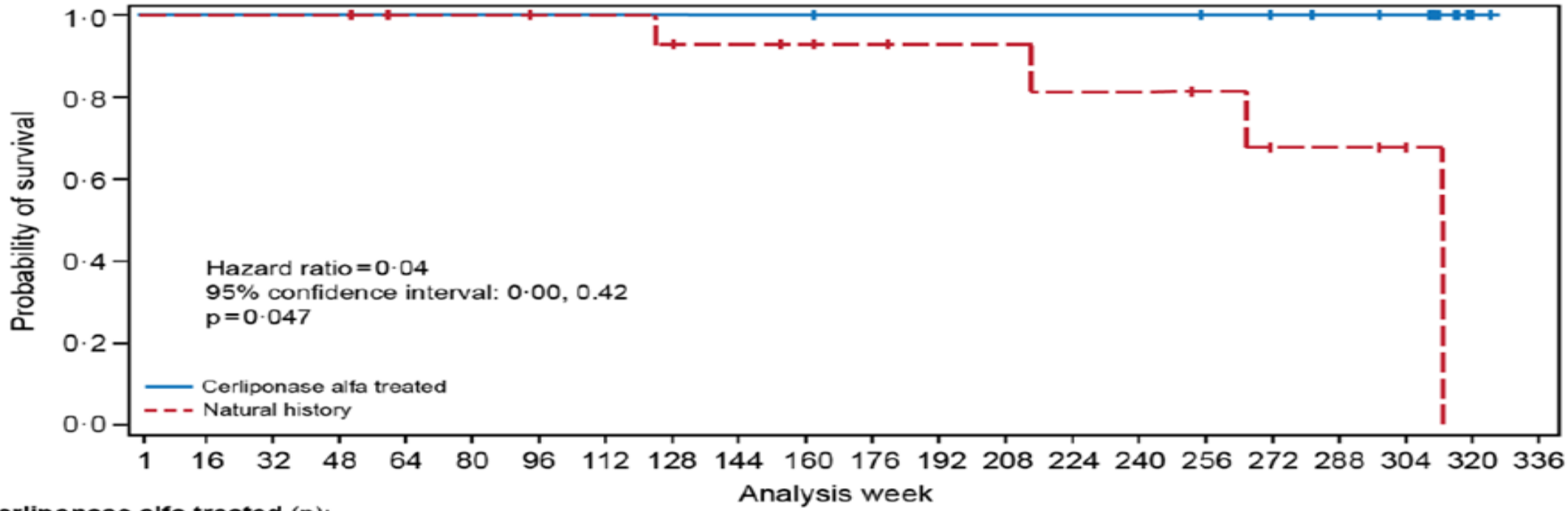



Link to – Clinical trials results

Abbreviations: FAS, Full analysis set; MAA, Managed access agreement; ML, Motor and Language; NH, Natural history;

# Survival 190-201/202

**Figure:** Age of death using KM estimation, Cox Model (1:1 matched NH and 190-201/202 population)




**Cerliponase alfa treated** (n):

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| At risk | 17 | 17 | 17 | 17 | 17 | 17 | 17 | 17 | 17 | 17 | 17 | 16 | 16 | 16 | 16 | 16 | 15 | 14 | 13 | 11 | 2 | 0 |
| Events | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Censored | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 2 | 3 | 4 | 6 | 15 | 17 |

**Natural history** (n):

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| At risk | 17 | 17 | 17 | 17 | 15 | 15 | 14 | 14 | 13 | 12 | 11 | 10 | 8 | 8 | 7 | 7 | 6 | 4 | 4 | 3 | 0 | |
| Events | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 4 | |
| Censored | 0 | 0 | 0 | 0 | 2 | 2 | 3 | 3 | 3 | 4 | 5 | 6 | 8 | 8 | 8 | 8 | 9 | 10 | 10 | 11 | 13 | |

Link to – Clinical trials results

Abbreviations: KM, Kaplan–Meier; NH, Natural history;

# Other clinical trials - Long-term safety data

**Table:** Summary characteristic of the long-term safety data studies

| | 190-501 (n=37) | 190-502 (n=27) | 190-504 (PASS) (n=48) |
|---|---|---|---|
| **Design** | Multicentre, post-marketing, observational, long-term safety study | Open-label, multicentre, multinational expanded access program/compassionate use | Multicentre, multinational, non-interventional (observational), post-authorisation safety study |
| **Population** | Participants with a confirmed diagnosis of CLN2 disease who intend to be or are currently being treated with cerliponase alfa | Patients with CLN2 disease (≥2 years of age), who cannot participate in a clinical trial | Participants with a confirmed diagnosis of CLN2 disease who intend to be or are currently being treated with cerliponase alfa |
| **Data cuts / Follow up** | 9th March 2023 – 104 weeks<br>Ongoing end data: 2030 | 7th September 2017 – 31 weeks | 26th April 2023 - 151 weeks<br>Ongoing end date 2024 |
| **Intervention** | Cerliponase alfa | | |
| **Study used in economic model** | No | | Yes |
| **Rational if not used in the model** | Additional information on the safety and tolerability of cerliponase alfa administration in patients with CLN2 disease was not used to inform the model | | |
| **Locations** | US | US, Germany, Italy, UK | Denmark, France, the Netherlands, Sweden, Italy, Germany, Romania, UK |
| **No of UK patients** | 0 | 6 | 7 |

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; PASS, Post authorisation safety study;

# Key issue: Baseline distribution across health states (1/2)

**Company comment (from previous committee meetings):**

- Starting age and baseline distribution informed by the subgroup of younger than 3 from Study 190-203 is expected to be reflective of the patients who will receive cerliponase alfa "In the near future"
- Starting age will be lower and ML score at treatment initiation will be higher than in the Study 190-203 full cohort and the MAA new patient cohort, due to: i) earlier diagnosis ii) shorter interval between diagnosis and treatment initiation iii) role of COVID-19 on delays to diagnosis and treatment initiation
- Analysis using data taken from clinical practice was not possible because COVID-19 may still be affecting diagnosis and all the data from the MAA database and clinical trials were affected by either cerliponase alfa not being available when people were diagnosed or COVID-19
  - ↳ Clinical experts estimate of "in Clinical practice 5-year time" gives the best estimate of a baseline distribution unaffected by COVID-19

**Clinical expert comment (from previous committee meetings):**

- Provided distributions based on data from their treatment centres
- People are being diagnosed earlier, with less disease progression due to improved training and education
- CE2: People will continue to diagnosed with ML scores below 5 without newborn genetic screening
- CE2: Is seeing more patients with a ML score of 5 or 6 in the past year due to earlier diagnosis
  - ↳ Current age of diagnosis is 3-4 years of ages (was previously close to 4-4.5 years)
- CE1: In the last 2 years they had not seen a patient diagnosed with an ML score below 5

 Abbreviations: CE, Clinical expert; MAA, Managed access agreement; ML, Motor and Language;

# Key issue: Baseline distribution across health states (2/2)

**EAG comment (from previous committee meetings):**

- The full cohort in study 190-203 and the subgroup younger than 3 may reflect a population younger and at an earlier point of disease progression than in clinical practice
  - ↳ [redacted] people in study 190-203 were presymptomatic and [redacted] were younger than 2 years old
  - ↳ Both have a small sample size, (full population, n=14, and subgroup younger than 3, n=8)
- Clinical advice
  - ↳ Diagnosis at an ML score of 6 is only likely if i) the child has an older sibling who has previously been diagnosed, ii) newborn screening for CLN2 is routinely conducted, or iii) there was very early onset of seizures
  - ↳ Committee preferred assumptions in HST12 (people initiating treatment would be equally distributed between health state 1 and 2 (ML score 6 and 5, respectively)) is not yet observed in current clinical practice and is unlikely to be observed in the next 5 years
- MAA new patient population is also unlikely to be an appropriate data source
  - ↳ May include people that couldn't access cerliponase alfa at the time of diagnosis
  - ↳ COVID-19 may have had an impact on delays to diagnosis and treatment initiation

**NHS England comment (from previous committee meetings):**

- A research project is underway, but it is uncertain if it will result in newborn genetic screening for CLN2 becoming routinely available


Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; EAG, External assessment group; HST, Highly specialised technology; MAA, Managed access agreement; ML, Motor and Language;

# Baseline ML Score distribution estimates for in 5-years time

- At the company's advisory board meeting clinicians were asked to provide estimates for baseline ML distributions in 5 years' time, assuming that newborn screening is not available

**Table:** Company advisory board baseline ML score distribution estimates

| Health State | ML Score | Most conservative | Realistic | Best achievable |
|---|---|---|---|---|
| **Age** | | - | - | -- |
| **1** | **6** | [redacted] | [redacted] | 70% |
| **2** | **5** | [redacted] | [redacted] | 25% |
| **3** | **4** | [redacted] | [redacted] | 5% |
| **4** | **3** | - | - | |
| **5** | **2** | - | - | |
| **6** | **1** | - | - | |

Link to – Unresolved key issues after ACM2



Abbreviations: ML, Motor and Language;

# Key issue: Evidence informing transition probabilities

**Company comment (from previous committee meetings):**

- Study 190-203 most closely reflects the population likely to receive cerliponase alfa in the near future
- The 'all patients' pooled dataset (matched to Study 190-901) was not preferred because
  - ↳ Cerliponase alfa was not a treatment option at diagnosis resulting in delayed treatment initiation
  - ↳ Some patients experienced progression while not receiving cerliponase alfa between the end of the EAP and the start of the MAA
  - ↳ Data from Study 190-201 includes patients who enrolled in the dose-escalation phase some of which experienced disease progression
  - ↳ COVID-19 delayed diagnosis and treatment for some

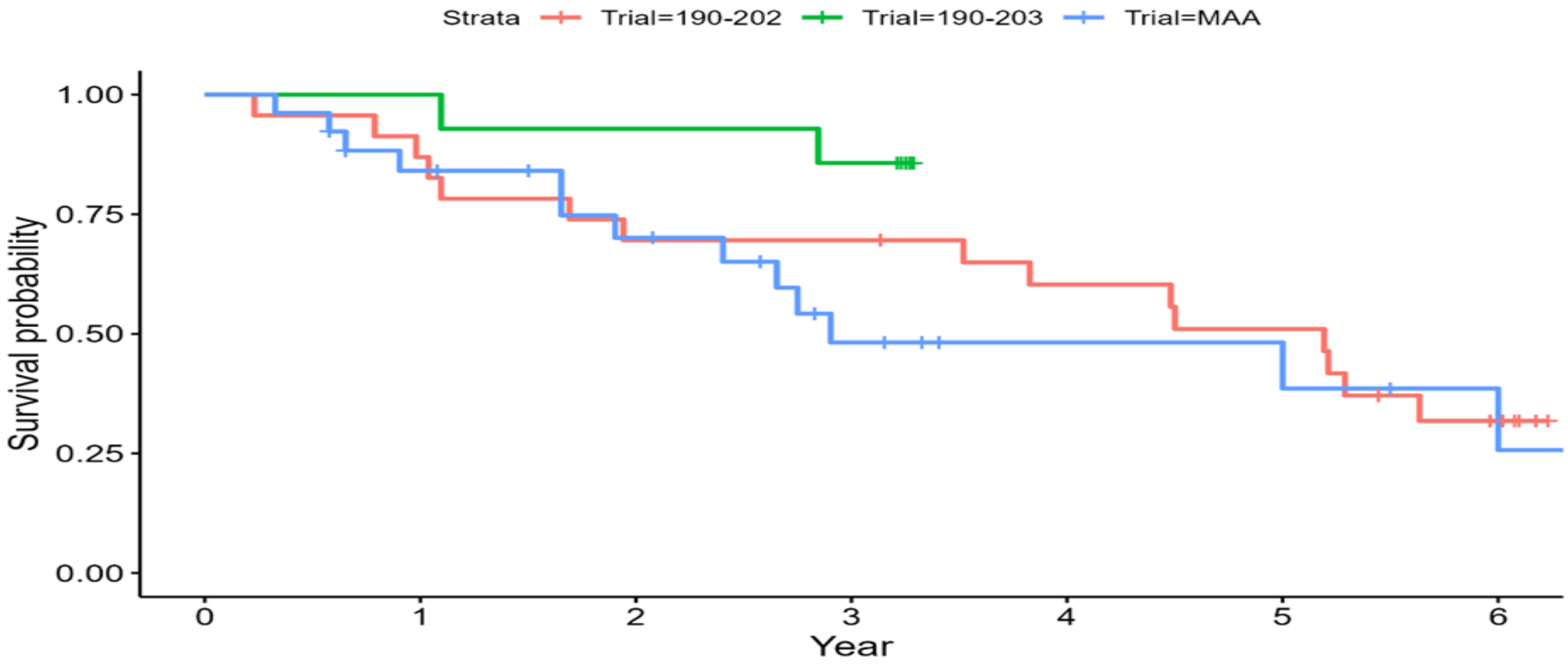
**EAG comment (from previous committee meetings):**

- Preferred evidence source is the 'all patients' pooled dataset (matched to Study 190-901)
  - ↳ Reflects most of the existing evidence due to sample size and overall length of follow-up
  - ↳ Acknowledges that it may introduce bias due to the delays and interruptions to treatment
- Study 190-203 has a smaller sample size and fewer number of events to inform transition probabilities and may not reflect the population in current and near future clinical practice and overestimate effectiveness
- Comparison of KM curves for a 2-point decline in ML score by study (Study 190-202, Study 190-203 and MAA) shows Study 190-203 had a notably slower decline than Study 190-202 and MAA.


Abbreviations: EAG, External assessment group; EAP, Expanded access program; KM, Kaplan–Meier; MAA, Managed access agreement; ML, Motor and Language;

# Time to unreversed 2-point decline or score of 0 in ML score by study

**Figure:** Time to a 2-point decline in ML score, by study




Abbreviations: MAA, Managed access agreement; ML, Motor and Language;

# Key Issue: Uncertainty around initial stabilisation (1/2)

**Company comment (from previous committee meetings):**

- Of the 8 patients aged ≤3 years in study 190-203, 7 had an ML score of 6 at baseline. Of these 5 had follow-up in study 190-504 and none of these patients had a change in ML score over 6 years follow-up
- Any transitions from ML score 6 in Study 190-203 reflect data for people who started with a ML score of 5

**EAG comment (from previous committee meetings):**

- Initial stabilisation assumptions are highly uncertain, and the evidence presented is insufficient
- Unclear how the company's assumption relates to the observed data
  - ↳ Data presented in Study 190-203 CSR suggests that [redacted]
- Company did not explain how information from Study 190-202 supports its stabilisation assumptions
  - ↳ [redacted] in study 190-202 who had a ML score of 6 [redacted]
- It is uncertain if the lack of progression by initial stabilisers is due to their age or other factors such as pre-symptomatic diagnosis
- The initial stabilisers progression rate beyond 6 years is also very uncertain given the lack of data

Link to – Proportion of people who enter the model in HS1 who are initial stabilisers
Link to – Initial stabiliser risk reduction

NICE Abbreviations: CSR, Clinical study report; EAG, External assessment group; ML, Motor and Language;

# Key Issue: Uncertainty around initial stabilisation (2/2)

**EAG comment (from previous committee meetings):**

- Clinical advice
  - ↳ It may be optimistic to assume that everyone with a starting ML score of 6 will be initial stabilisers
  - ↳ It is not unreasonable to assume that the initial stabilisation persists for 6 years
  - ↳ The company's initial stabilisers progression rate beyond 6 years assumption is clinically plausible

**Clinical expert comment (from previous committee meetings):**

- CE1: Suspects at least 80% of people that start treatment with an ML score of 6 will be initial stabilisers
- CE2: Agrees with the company's initial stabiliser assumptions at ACM1
- Some patient who start having cerliponase alfa in HS1 would be pre-symptomatic with normal motor and language function and some would have symptoms and near-normal motor and language function
  - ↳ Only those who are pre-symptomatic would be likely not to progress to HS2 (ML score of 5) in 6 years

Link to – Proportion of people who enter the model in HS1 who are initial stabilisers
Link to – Initial stabiliser risk reduction

 Abbreviations: ACM, Appraisal committee meeting; CE, Clinical expert; EAG, External assessment group; HS, Health state; ML, Motor and Language;