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

For Zoom –information
REDACTED

Highly Specialized Technology Appraisal Committee [10 July 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; HST, Highly specialised technology;

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

- ✓ **Recap of ACM1, ACM2 and ACM3**
- ❑ Key Issues
- ❑ Comments on the draft guidance document
- ❑ Cost effectiveness

NICE National Institute for Health and Care Excellence

History of the appraisal

November 2019 MA Entry (HST12)	• Cerliponase alfa received a positive recommendation within the context of a MAA • The previous appraisal identified several issues that meant that a MAA was needed ↳ 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ACM3	• After ACM3 NHS England and the company agreed commercial terms for prevalent (existing) patients, draft guidance issued
ACM4	• To discuss consultation comments and reconsider the cost-effectiveness for incident (new) patients

NICE

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

Managed Access and Innovative Medicines Fund principles

What is a managed access agreement?

Managed access gives people temporary access to promising new treatments that might not be recommended because of uncertainties about their clinical or cost effectiveness. It allows for additional evidence to be collected to reduce that uncertainty and also helps ensure value for money for taxpayers so long as they are potentially cost effective.

What happens at the end of managed access?

Evidence is collected on the treatment until the end date specified in the managed access agreement. After this, the committee reviews the guidance and decides whether to recommend the treatment for routine use in the NHS.

If the evidence shows that the treatment is not a cost-effective use of NHS resources, it will not be recommended.

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 ↳ 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 • 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) • The recommended dosage for those >2 is 300mg every other week (annual cost £522,782) • Company has a confidential PAS discount in place

NICE

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

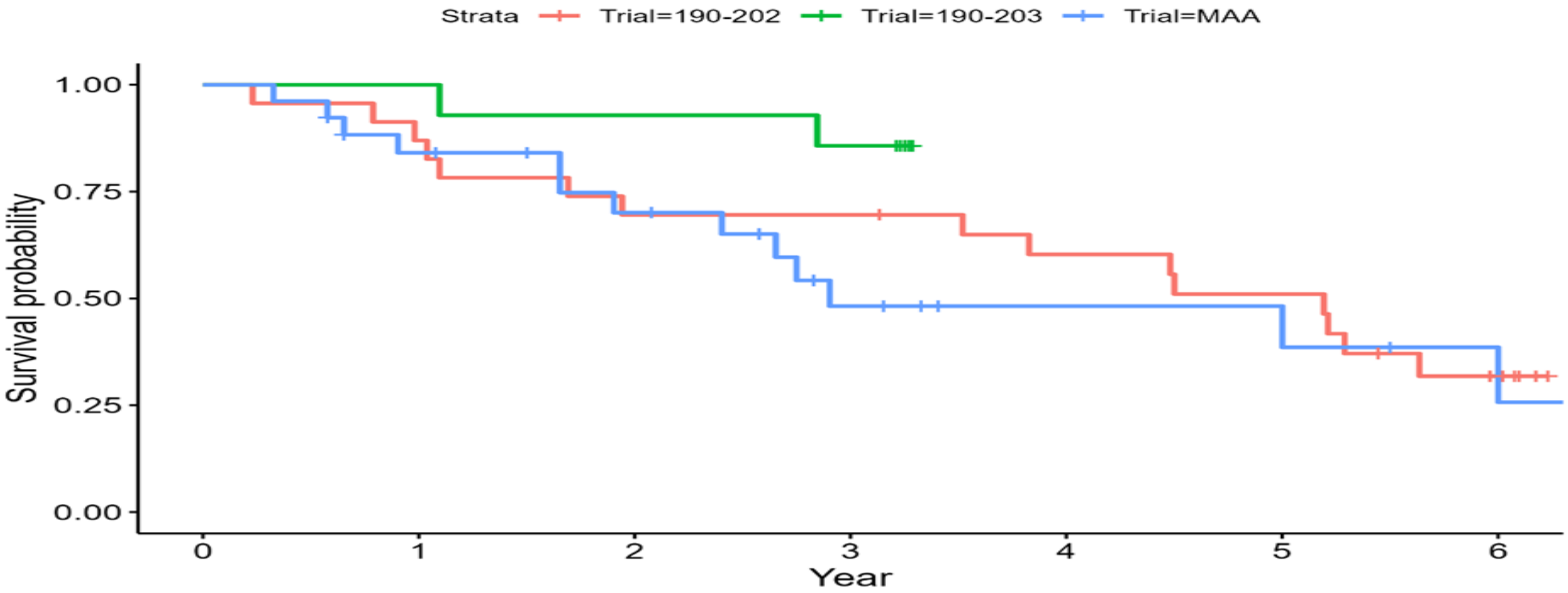
* See appendix – Time to unreversed 2-point decline or score of 0 in ML score * See appendix – Survival

* 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

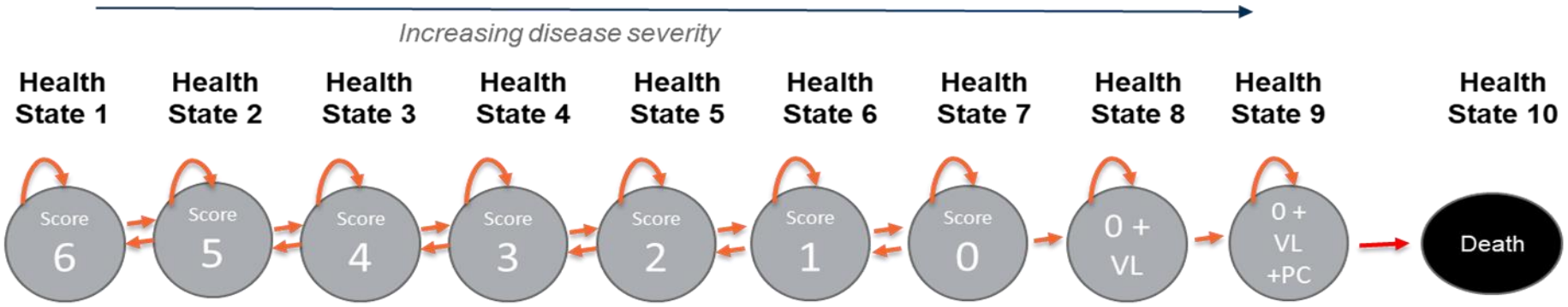


Committee conclusion post ACM3

- 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;

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 ACM3 (1/2)

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 A treatment effect on the proportion of patients incurring the costs of progressive symptoms was plausible ↳ The company's estimates of the proportions in each arm was suitable for decision making
Baseline distribution across health states	Informed by the clinician estimate of the realistic baseline distribution in 5 years' time (From company's December 2024 advisory board)
Proportion of people who enter the model in HS1 who are initial stabilisers	80%
Initial stabiliser risk reduction	50%
Evidence informing transition probabilities	Pooled dataset*, including data from the MAA
Robustness of transition probability estimates in HS1-7	The company's method to estimate transition should be used Backward transitions to healthier HSs should be allowed

*Committee acknowledged that using the pooled data may be conservative. To account for this, the committee concluded that the QALY weighting should be increased by 0.2.

Abbreviations: ACM, Appraisal committee meeting; HS, Health state; MAA, Managed access agreement;

Committee preferred assumptions post ACM3 (2/2)

Issue	Committee preferred assumption (Incident and prevalent population)
Vision loss progression	Cerliponase alfa has no impact on vision loss
Treatment discontinuation	For modelling cost-effectiveness, it should be assumed treatment stops when people reach HS7 (ML score of 0) ↳ But in clinical practice treatment should not be stopped just because a person has reached HS7
Health state utilities	HS utilities from Gissen et al. (2021) should be used
Treatment initiation	There should be no starting rules*
Other issues	Costs for background care, ECG monitoring (in line with the SmPC) and psychiatric and behavioural support should be included Neuro-disability mortality should be included in all health states.

*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

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

Draft guidance recommendations

The committee took into account the condition's rarity, severity and the effect of cerliponase alfa on quality and length of life. But using the proposed price of the medicine, the most likely cost-effectiveness estimate is not within what NICE considers an acceptable use of NHS resources.

Recommendations

1.1 Cerliponase alfa is not recommended, within its marketing authorisation, for treating neuronal ceroid lipofuscinosis type 2 (CLN2) also known as tripeptidyl peptidase 1 deficiency.

1.2 This recommendation is not intended to affect treatment with cerliponase alfa that was funded with managed access before final guidance was published. People already having cerliponase alfa for treating CLN2, or who start cerliponase alfa before the end of the managed access period (December 2025), can continue with treatment until they and their NHS healthcare professional consider it appropriate to stop. This decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2;

Draft guidance consultation comments

Comments received from:

- Company – BioMarin
- Batten Disease Family Association (BDFA)
- Two clinical experts
- Two patient experts
- Two consultees (Newcastle upon Tyne Hospitals NHS Foundation Trust – paediatric IMD service for North East England and North Cumbria & University Hospitals Bristol and Weston Foundation Trust)
- Online comments from 6 individuals

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

- ❑ Recap of ACM1, ACM2 and ACM3
- ✓ **Key Issues**
- ❑ Comments on the draft guidance document
- ❑ Cost effectiveness

NICE National Institute for Health and Care Excellence

Key issue: Diagnosis and newborn screening (1/2)

ACM3 conclusions

- Clinical experts explained that currently there is no screening programme for CLN2 so unless a child has an older sibling with CLN2 they will only be diagnosed after symptoms appear
- NHS England stated that a research project is underway, but it is uncertain if it will result in NBS becoming routinely available

Company response

- The significant progress made in the awareness and early diagnosis of CLN2 is not adequately reflected
- Delays in diagnosis are a key factor negatively impacting the cost-effectiveness of cerliponase alfa
  - ↳ This appraisal should not be penalised for diagnostic shortcomings so adjustments should be made for the challenges that surround enabling early diagnosis
- Attempts to support early diagnosis have been met with significant bureaucratic and systemic barriers and limited collaboration
  - ↳ Before the MAA NHSE independently committed to implementing a diagnostic pathway but declined the company's offer to sponsor diagnostic services
- Committee should consider the direction of travel in relation to NBS
  - ↳ Experts at the December 2024 advisory board highlighted with growing likelihood that NBS could be implemented in England within the next 5 to 10 years
- NBS has been shown to be effective for other conditions
- NBS is unlikely to be implemented if cerliponase alfa receives a negative recommendation

Abbreviations: ACM, Appraisal committee meeting; CLN2, Neuronal ceroid lipofuscinosis type 2; MAA, Managed access agreement; NBS, Newborn screening;

Key issue: Diagnosis and newborn screening (2/2)

Patient expert comment

- NBS has been delayed for too long and needs to be made available

Consultee comment

- The Generation Study will now provide a route to screening for CLN2 – even if this is not subsequently adopted as a universal offer
  - ↳ The recommendation in the draft guidance means there will be no treatment available for children identified through the Generation Study

Online comment

- Introduction of easier genetic epilepsy panel testing has contributed to earlier diagnoses

EAG comment

- The EAG and committee have taken steps to consider the impact of earlier diagnosis including:
  - ↳ Modifying the baseline distribution across ML scores (Committee preferred baseline distribution assumes the percentage of children starting treatment with a ML score of 6 is higher than in HST12)
  - ↳ Allowing more favourable outcomes for children diagnosed before symptoms develop including longer periods of initial stabilisation, and slower long-term decline

NICE technical team comments

- NHS 10-year plan aims to improve genetic screening, but unlikely in the next 5 years.

NICE

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; EAG, External assessment group; HST, Highly specialised technology; ML, Motor and Language; NBS, Newborn screening;

Key issue: Baseline distribution across health states (1/3)

ACM3 conclusions

- The 'most realistic' estimate of ML score distribution at the time of diagnosis in 5 years' time from the company's advisory board should be used in decision making
- The committee considered it had not been presented with evidence to suggest it was plausible 70% of people will start treatment in HS1 (ML score 6)

Company response

- The "best achievable" distribution from the December 2024 company advisory board should be used
- Given the increasing likelihood of NBS implementation and the observed pattern of earlier diagnosis the 'best achievable' estimate (70% start at ML 6) is a more realistic projection
- NICE's approach is not supported by clinical expertise
  - ↳ It excludes the possibility for continued improvements in the absence of NBS, as well as the potential impact of NBS altogether

Clinical expert comments

- CE1: In the last 3 years the children that have started treatment have all had ML scores of 5 or 6
- CE2: Most children seen recently have had a ML score of 5 or 6

EAG comment

- The company has not provided additional evidence to support the argument that the 'optimistic' distribution from the advisory board is reflective of clinical practice in five years' time

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

Key issue: Baseline distribution across health states (2/3)

- 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 (Committee preferred)	Best achievable (Company preferred)
Age		-	-	--
1	6	[redacted]	[redacted]	70%
2	5	[redacted]	[redacted]	25%
3	4	[redacted]	[redacted]	5%
4	3	-	-	
5	2	-	-	
6	1	-	-	

Abbreviations: ML, Motor and Language;

Key issue: Baseline distribution across health states (3/3)

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)	Study 190-203 (N=14)	MAA new patients (N=24)	Original HST12	EAG CE *"Current clinical practice"*	EAG CE (Clinical practice in 5-year time)	*CE (Patients treated at GOSH) (N=19)**	*ACM1 CE*
Age		2	-	-	4	4.5	3.5	*26.3%**<4 73.6% 4 - 4 yrs 11 months*	-
1	**6**	87.5%	50.0%	18.2%	50%	15%	50%	10.5%	28.5%
2	**5**	12.5%	7.1%	13.6%	50%	45%	35%	10.5%	28.5%
3	**4**	-	21.4%	45.5%	-	30%	12.5%	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

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 (1/3)

ACM3 conclusions

- After considering the advantages and disadvantages of both the data from Study 190-203 and the pooled data, the pooled data including data from the MAA should be used for decision making
  - ↳ The pooled data may result in a conservative estimate of efficacy of, which was taken into account
- Reported that clinical experts advised that up to 20 years in HS1 was possible, but likely overly optimistic

Company response

- The clinical experts at the December 2024 advisory board confirmed Study 190-203 most closely reflects current diagnosis, referral, and treatment
- NICE appears to have conflated the assessment of existing and future patients by using the most negative perspective on transition probabilities
- Progress in achieving early diagnosis should be captured in the transition probabilities
- The pooled data is outdated, confounded, and non-representative and results in a distorted and clinically implausible representation of the treatment effect
- The Study 190-201 and MAA cohorts are not representative of children who start treatment today
  - ↳ Study 190-201 include children who had already experienced a long duration post diagnosis and that did not receive the disease management provided in the NHS today
  - ↳ Children in Study 190-201 transitioned into the MAA so biases are carried into the pooled data
  - ↳ The MAA cohort included children whose diagnosis or treatment was delayed due to COVID-19 or who had to wait for HST12 to conclude before starting treatment

Abbreviations: ACM, Appraisal committee meeting; HS, Health state; HST, Highly specialised technology; MAA, Managed access agreement;

Key issue: Evidence informing transition probabilities (2/3)

Company response

- Committee should consider and clarify what data in the pooled dataset was impacted by COVID-19
- The impact of the pandemic should be reflected in the appraisal as a material factor affecting the integrity and interpretation of the evidence base
- The draft guidance's significantly underplays the severe and lasting impact of the COVID-19 pandemic
  - ↳ It fundamentally impaired early identification, diagnosis, referrals access to services, and specialist support, all of which are critical for a condition where time to treatment determines life trajectory
  - ↳ The impact of the pandemic has been highlighted and corroborated by clinical experts
- Volume of data should not be prioritised over relevance

Patient group comment

- The pooled data does not reflect current clinical practice where earlier diagnosis is more common which leads to better treatment outcomes
- The pooled data dose not capture the effectiveness of cerliponase alfa due to the impact of the pandemic

Clinical expert comments

- CE1 and CE2: The patients starting treatment now are in much better health than those in the trials and MAA cohort and would be expected to experience better treatment outcomes
- CE2: Is concerned that mixed data from the past is being used to interpret the future population

 Abbreviations: CE, Clinical expert; MAA, Managed access agreement;:

Key issue: Evidence informing transition probabilities (3/3)

Clinical expert comments

- CE2: Some children diagnosed with ML score of 5 & 6 remain independently ambulant at 6-7 years of age

Consultee comments

- Cerliponase alfa has been shown to be more effective in children diagnosed early → A patient who started treatment at 18 months who remains fully ambulant and communicative at age 9 years

Online comments

- When treatment is started earlier the disease burden can be less

EAG comments

- Study 190-203 might better represent future patients however it:
  - ↳ Reduces the size of the evidence base so reduces confidence in estimated transition probabilities
  - ↳ Can not inform the full set of transition probabilities due to the lack of data for transitions between more severe HSs, such as between HS 6 and 7 → So even in the analyses using Study 190-203, three transitions were informed by probabilities estimated from the 'all patients' pooled dataset
- Expected time spent in HS1 (ML score 6) (for someone starting treatment in HS1)
  - ↳ Using pooled data: 19.6 years and using Study 190-203 data: 34.47 years
- Expected time spent in HS1 (ML score 6) (for entire modelled cohort)
  - ↳ Using committee's preferred assumptions: 12.66 years and using the Company's preferred assumptions (Baseline distribution: Best achievable from 2024 advisory board Evidence source for the transition probabilities: Study 190-203): 27.40 years

Abbreviations: CE, Clinical expert; HS, Health state; ML, Motor and Language;

Key issue: Treatment initiation and discontinuation

ACM3 conclusions

- Ideally there would be no starting rules → But 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.
- Treatment should continue until the person's family/carers and NHS healthcare professional decide it is appropriate to stop

Patient expert comment

- PE1: Is vehemently opposed to introducing starting and stopping criteria →Their two daughters started treatment at different stages, but both benefited hugely → Children should not stop treatment because they have reached a threshold for cost effectiveness

Consultee comment

- Consultee 1: Is concerned that an inability to agree starting and stopping criteria between NICE, patient groups and clinical experts has resulted in cerliponase alfa not being available for the group likely to experience significant QALY gains (Children under the age of 3)
- Consultee 2: If the decision was between stopping cerliponase treatment at HS 6, with the benefit of being able to start treatment for those in higher health states, then this could be discussed

Online comment

- To allow targeted access to cerliponase alfa there should be a frank dialogue/consideration about starting treatment criteria →There should be a right to appeal for cases not deemed eligible

Abbreviations: ACM, Appraisal committee meeting; HS, Health state; PE, Patient expert; QALY, Quality-adjusted life year;

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

- ❑ Recap of ACM1, ACM2 and ACM3
- ❑ Key Issues
- ✓ **Comments on the draft guidance document**
- ❑ Cost effectiveness

NICE National Institute for Health and Care Excellence

Comment: Insufficient recognition of ultra-rare disease context

Draft guidance

- States that CLN2 is a rare disease (It is estimated that, in the UK, about 3 to 6 children are diagnosed each year and currently about 30 to 50 children are living with the condition)
- Cerliponase alfa is being appraised under the HST programme, which is only used for very rare conditions
  - ↳ The HST programme uses a higher cost per QALY level, that can be increased based on the size of the incremental QALY gain, and it allows committee to consider additional factors in its deliberations

Company response

- CLN2 is an ultra-rare disease this should be better reflected in the guidance
  - ↳ The guidance does not reflect the constraints of evidence generation for ultra-rare diseases
  - ↳ The small sample size in the data is characteristic of the small population and low incidence
- Collecting data on non-neurological outcomes is difficult
  - ↳ In the natural history cohort patients were too unwell to undergo some assessments but, in the MAA psychological tools could be applied, which shows the natural history of the disease has changed
- NICE should accept higher uncertainty →The existing uncertainty can not be resolved by further data collection or alternative trial designs → Conducting a RCT would not have been possible or ethical

Patient group comment

- The draft guidance suggest that the committee did not fully appreciate the ultra-rare nature of CLN2
- The committee set unrealistic expectation for the MAA that the limited patient population cannot provide

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

Comment: Insufficient recognition of ultra-rare disease context

Patient group comment

- Section 6.2.34 of the method's manual states *"The committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult because they are: rare diseases, for use in a population that is predominantly children (under 18 years old), innovative and complex technologies"* → For this appraisal all three of these criteria apply

Patient expert comment:

- PE1: Believes that due to the small patient population the HST appraisal process is not able to accurately assess cerliponase alfa.
- PE2: Cerliponase alfa provides clear benefits it could be argued that NICE should be extending the treatment timescale to collect long term evidence

EAG comment:

- It is not clear why the company considers that the draft guidance does not sufficiently recognise the limitations of evidence generation in the context of ultra rare diseases
  - ↳ EAG and Committee have used data from a range of sources to inform the treatment effect
- Agrees that an RCT is infeasible for this condition, and has never suggested that one was required, nor has it criticised the use of a natural history cohort as a comparator group

Abbreviations: EAG, External assessment group; HST, Highly specialised technology; PE, Patient expert; RCT, Randomised controlled trial;

Comment: Description of the Study 190-203 data

Draft guidance

- Reports that the clinical experts explained that people who are diagnosed earlier and start treatment earlier with less disease progression benefit the most from cerliponase alfa
- Describes how committee have incorporated an “initial stabiliser” assumption in its base case which assumes that pre-symptomatic patients treated with cerliponase alfa showed substantially improved outcomes compared with those treated after symptom onset
- Reports the EAG’s concern that applying the initial stabiliser assumptions to data from Study 190-203 may double-count the benefits of starting treatment earlier with less progressed disease

Company response

- Committee have failed to acknowledge that Study 190-203 demonstrates that pre-symptomatic patients treated with cerliponase alfa showed substantially improved outcomes compared with those treated after symptom onset

Consultee comment

- The limitations of Study 190-203 (small number and limited follow up) is not being fully addressed

Abbreviations: EAG, External assessment group

Comment: Non-reference case analysis (1/2)

Draft guidance

- At ACM2 the committee noted that the company:
  - ↳ Removed costs related to health state, vision loss, psychiatric and behavioural support and residential care from both arms in its updated base case.
  - ↳ Stated that treatment with cerliponase alfa is associated with longer-term survival that results in increased background care costs that do not represent direct, intrinsic consequences of treatment.
  - ↳ Only presented its base case with background care costs removed (The NICE manual states that such analysis should be considered alongside the reference case analysis)
- At ACM2 the committee concluded it had not been provided with evidence or a clear rationale for the removal of the background costs. So, only the reference-case analyses should be used for decision making
- At ACM3 the committee noted that the additional scenarios presented by the company before the third committee meeting included background care costs in line with its preferred modelling assumption

Company response

- The draft guidance implies an absence of rationale or evidence, does not accurately reflect the content and intent of the submission before ACM2

Comment: Non-reference case analysis (2/2)

Company response

- The rationale for excluding background costs were clearly documented in the company submission ahead of ACM2, including detailed justification based on the nature of CLN2 disease and associated high-cost care, even in the absence of active treatment.
  - ↳ The specific costs excluded were stated and it was explained that these costs reflect longer survival with cerliponase alfa, rather than direct consequences of treatment.
- A version of the company base case including background care costs was not submitted ahead of ACM2
  - ↳ However, the implications of excluding background costs were addressed through the corresponding committee base case scenarios, which were reported with and without background care costs.

EAG comment

- The committee has considered the company's justification for excluding background care costs and concluded it did not warrant the exclusion of the background care costs from the base-case analysis
- Provided ICERs including and excluding background care costs

NICE

Abbreviations: ACM, Appraisal committee meeting; CLN2, Neuronal ceroid lipofuscinosis type 2; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio;

Comment: Severity and treatment impact representation

Draft guidance

- The committee recognised that CLN2 is a rapidly progressive and devastating condition. It concluded that CLN2 has a substantial impact on the lives of children with CLN2 and their families.
- Clinical experts explained that people having cerliponase alfa will live longer and remain in much better health than people who only have supportive care

Company response

- The draft guidance does not fully convey the devastating nature of CLN2 disease and does not adequately reflect the transformative impact of cerliponase alfa
  - ↳ Committee has taken a more conservative approach which undermines the significant suffering experienced by patients and families
- Patient experts described children not only living longer, but in some cases leading lives that closely resemble those of unaffected peers
- Without treatment, patients lose mobility and become non-mobile around 6 years old and as the disease progresses, they will require feeding tubes or gastrostomy, and usually die between the ages 8 and 12

Patient group comment

- The draft guidance fails to describe the true devastating nature and clinical course of untreated CLN2
- The committee has not fully considered critical evidence (including a survey of parents and teachers that demonstrate the benefits of cerliponase alfa and the devastating impact of CLN2)
- The draft guidance overemphasises uncertainty and fails to consider the lack of alternative treatments

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2;

Comment: Alternative data sources (1/2)

Patient expert comment:

- PE1: The appraisal has focused on ML changes and does not capture all benefits of cerliponase alfa.
- PE1: The truest and most meaningful measure of the impact on a child's quality of life are the testaments of their life with their family, their enjoyment and engagement at school, the hobbies they enjoy, the activities they can access and how much more of a pain-free life they are able to live
  - ↳ Cerliponase alfa allows children to travel, enjoy special activities and spend time with their family
- PE1: Input from parents should be included in a measured and quantifiable way
  - ↳ Real world data included in the BDFA submission demonstrates the benefit cerliponase alfa has on a child's schooling and enjoyment
- PE2: Real world data should be used due to CLN2 being a rare disease and the small population
- PE2: Data from trials and the MAA may not reflect reality
  - ↳ Assessments during the MAA were conducted by someone the child did not know and took place either in the early morning after hours of traveling or after a 4-hour long brain infusion

Clinical expert comments:

- CE2: NICE should engage with clinicians who are continuing to collect data for children who started treatment with higher ML scores

Consultee comments:

- Cerliponase alfa should be made available for children under the age of 3 and with an ML score of 6 to allow for ongoing monitoring and long term effectiveness data collection

NICE

Abbreviations: BDFA, Batten Disease Family Association; CE, Clinical expert; CLN2, Neuronal ceroid lipofuscinosis type 2; MAA, Managed access agreement; ML, Motor and Language; PE, Patient experts:

Comment: Alternative data sources (2/2)

Online comments:

- An array of clinical improvements have been undervalued in this review (e.g. seizure control, pressure injury avoidance, reduction in admission and PEG costs)
- The reduced cost of care due to keeping children living well and independently for longer has not been calculated
- Insufficient weighting has been given to the real-world experiences put forward by parents, siblings, grandparents and carers
    - ↳ More time is needed to collect the data necessary to make a well-informed decision

 Abbreviations: PEG, Percutaneous Endoscopic Gastrostomy;

Comment: Carer and family benefits

Draft guidance

- The committee noted that QALY gains experienced by carers and siblings were accounted for in the model
  - ↳ The committee accepted the company's approach to modelling caregiver and sibling disutility
- The committee noted that section 6.2.24 of NICE's manual states that QALY weighting should be based on the QALYs gained over the lifetime of the patient
  - ↳ So, only the QALYs gained by the person having cerliponase alfa should be used to inform the QALY weighting

Patient group comment

- Cerliponase alfa does not just help the child it reduces the burden on parents and siblings
  - ↳ It could mean parents might not have to care for their children as intensively or grieve as early

Patient expert comment

- QALY gains associated with carers and sibling should be included in the QALY weighting calculation

Abbreviations: QALY, Quality-adjusted life year;

Comment: Impact of cerliponase alfa on vision

Draft guidance

- Clinical experts advised that cerliponase alfa would only improve vision loss if it was delivered into the eye by intravitreal injections, which is not approved under the current marketing authorisation
- The committee noted it had not seen evidence to support the assumption that cerliponase alfa delays vision loss → It concluded that it should be assumed that cerliponase alfa has no impact on vision loss

Patient group comment

- Committees preferred assumption underestimates the benefit of cerliponase alfa
  - ↳ Some children over the age of 10 receiving cerliponase alfa have kept their vision

Clinical expert comment

- The benefits of cerliponase alfa being delivered by intravitreal injections have not been considered

Additional comments (1/2)

Company response:

- Cerliponase alfa is currently available in Scotland (under a data collection agreement) which raises a significant equity concern
  - ↳ It is possible cerliponase alfa will be unavailable to patients with the same clinical need in England
  - ↳ Families could relocate to Scotland to access treatment

Patient group comment

- The draft guidance downplays non-neurological benefits such as the impact of cerliponase alfa on seizures, pain, or the need for feeding tubes
  - ↳ Clinical experts and patients have provided evidence that they have seen improvements or stabilisation in these areas
- Treatment centres have developed specialised infrastructure, sterile treatment environments, and multidisciplinary teams dedicated to administering cerliponase alfa
  - ↳ These gains will be reversed if the recommendation in the draft guidance remain unchanged

Patient expert comment:

- PE1: Children with low ML scores should not be viewed as leading a poor quality of life
  - ↳ Families adapt and ensure their lives are surrounded by different stimuli and exciting adventures, which are accessible and individualised

 Abbreviations: PE, Patient expert;

Additional comments (2/2)

Patient expert comment:

- PE1: A negative recommendation would
  - Be hugely detrimental to how the UK is viewed as a potential market for new technologies
  - Mean time, money and resource used to establish the 7 treatment centres would be wasted

PE1: The limiting factor of 30 QALY's is detrimental to the entire process

  - It has been widely agreed that Brinuera would go beyond 30 additional QALYs due to it's transformative results but the cap set at 30 cannot be moved, it's not a true reflection of the true impact of the drug*

- PE2:The maximum acceptable ICER has not been increased in many years and needs addressing
  - Has committee considered increasing the threshold and has NICE asked the government to increase the threshold for rare diseases?

*Company base case results in less than 30 QALYs

Comment: Draft guidance recommendations (1/3)

Draft guidance

- Cerliponase alfa is not recommended within its marketing authorisation
  - ↳ People already having cerliponase alfa, or who start before the end of the MA period (Dec 2025), can continue until they and their NHS healthcare professional consider it appropriate to stop

Patient group comment

- The negative draft recommendation for children diagnosed after December 2025 creates profound inequity, denying future patients a proven treatment that slows disease progression and enhances quality of life
- The guidance fails to consider the immense clinical, emotional, and operational burden that will result from denying treatment to newly diagnosed children with CLN2
  - ↳ Clinicians and nurses who have witnessed the tangible benefits of cerliponase alfa would face the ethical distress of being unable to offer this treatment to future patients
- The draft guidance fails to assess the equality impact on disabled children diagnosed post-2025
  - ↳ CLN2 qualifies as a disability and only giving access to children diagnosed before 31 December 2025 constitutes indirect disability and age discrimination

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; MA, Managed access; ML, Motor and Language;

Comment: Draft guidance recommendations (2/3)

Patient expert comment

- PE1: A cutoff date for accessing treatment is inhumane.
- PE1: Children with CLN2 should be allowed the same equity in accessing a treatment for their condition, like children with less rare conditions are routinely offered.
- PE2: Making cerliponase alfa available for some children but not others should never be considered

Clinical expert comment

- CE1: The draft guidance recommendation discriminates against patients with neuro and visual disability

Consultee comments

- Consultee 1: The draft guidance means those most likely to benefit (Children under 3 years old) will be at a significant disadvantage because they will not be able to access a potentially life changing treatment
- Consultee 2: Based on the draft guidance there will be inequity in provision with patients with identical conditions being treated differently, dependent upon their date of diagnosis

Online comments

- It is unreasonable and unethical to ask clinicians to withhold treatment from one group but treat another based upon an arbitrary deadline
- The draft guidance unlawful discrimination based on the time of diagnosis.
    - ↳ Not recommending treatment for patients from December 2025 will mean that patients will not be able to access a treatment which has been shown to slow disease progression

Abbreviations: CE, Clinical expert; PE, Patient expert;

Comment: Draft guidance recommendations (3/3)

Online comment:

- There is discrimination if the treatment is provided for some children but not others and this decision is based on uncertainty, insufficient evidence and assumptions about the likely effectiveness of the treatment
- Aspects that should be considered to ensure implementation is equitable and non-discriminatory
  - ↳ Age: Ensure age-based eligibility criteria are clinically justified and don't unfairly exclude older children who could benefit. Age cut-offs should be evidence-based, not arbitrary.
  - ↳ Disability: CLN2 is a severe disability. Ensure access to cerliponase alfa and related support services is equitable, regardless of the severity of the disability or other co-existing conditions.
  - ↳ Race: CLN2 affects all races, ensure that diagnostic pathways and access to treatment are equally available to all racial groups. Address any potential disparities in diagnosis or referral patterns
  - ↳ Socioeconomic status: Consider the potential for socioeconomic barriers to accessing treatment, such as travel costs to specialist centres. Ensure that financial support and logistical assistance are available to families regardless of their income

NICE technical team comments:

- Managed access agreements are special time-limited arrangements to allow patients to access medicines that are promising but uncertain with respect to clinical and cost effectiveness. All managed access agreements are reviewed at the end of the managed access period and if cost-effectiveness cannot be demonstrated, routine access for patients not already receiving and benefitting from the treatment is not possible in the NHS.

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2;

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

- ❑ Recap of ACM1, ACM2 and ACM3
- ❑ Key Issues
- ❑ Comments on draft guidance document
- ✓ **Cost effectiveness**

NICE National Institute for Health and Care Excellence

Cost-effectiveness results

- 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

Abbreviations: ICER, Incremental cost-effectiveness ratio;

Cost-effectiveness – Individual scenarios (1/2)

Table: Cost-effectiveness results committee preferred assumptions at ACM3 and individual scenarios

Technology	Total costs (£)	Total QALY	Inc costs (£)	Inc QALY	ICER (Background care costs)		CoE threshold (Carer / sibling disutilities)		LY in HS1 (ML 6)*
					Included	Excluded	Included	Excluded	
Committee preferred assumptions at ACM3									
SoC	[redacted]	-0.63							0.35
Cerliponase alfa	[redacted]	9.03	[redacted]	9.65	[redacted]	[redacted]	[redacted]	[redacted]	12.66
Scenario 1: Transition probabilities from Study 190-203									
SoC	[redacted]	-0.50							0.49
Cerliponase alfa	[redacted]	12.26	[redacted]	12.76	[redacted]	[redacted]	[redacted]	[redacted]	24.77
Scenario 2: 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]	[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 – Individual scenarios (2/2)

Table: Cost-effectiveness results individual scenarios

Technology	Total costs (£)	Total QALY	Inc costs (£)	Inc QALY	ICER (Background care costs)		CoE threshold (Carer / sibling disutilities)		LY in HS1 (ML 6)*
					Included	Excluded	Included	Excluded	
Scenario 1 and 2: 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]	[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;

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

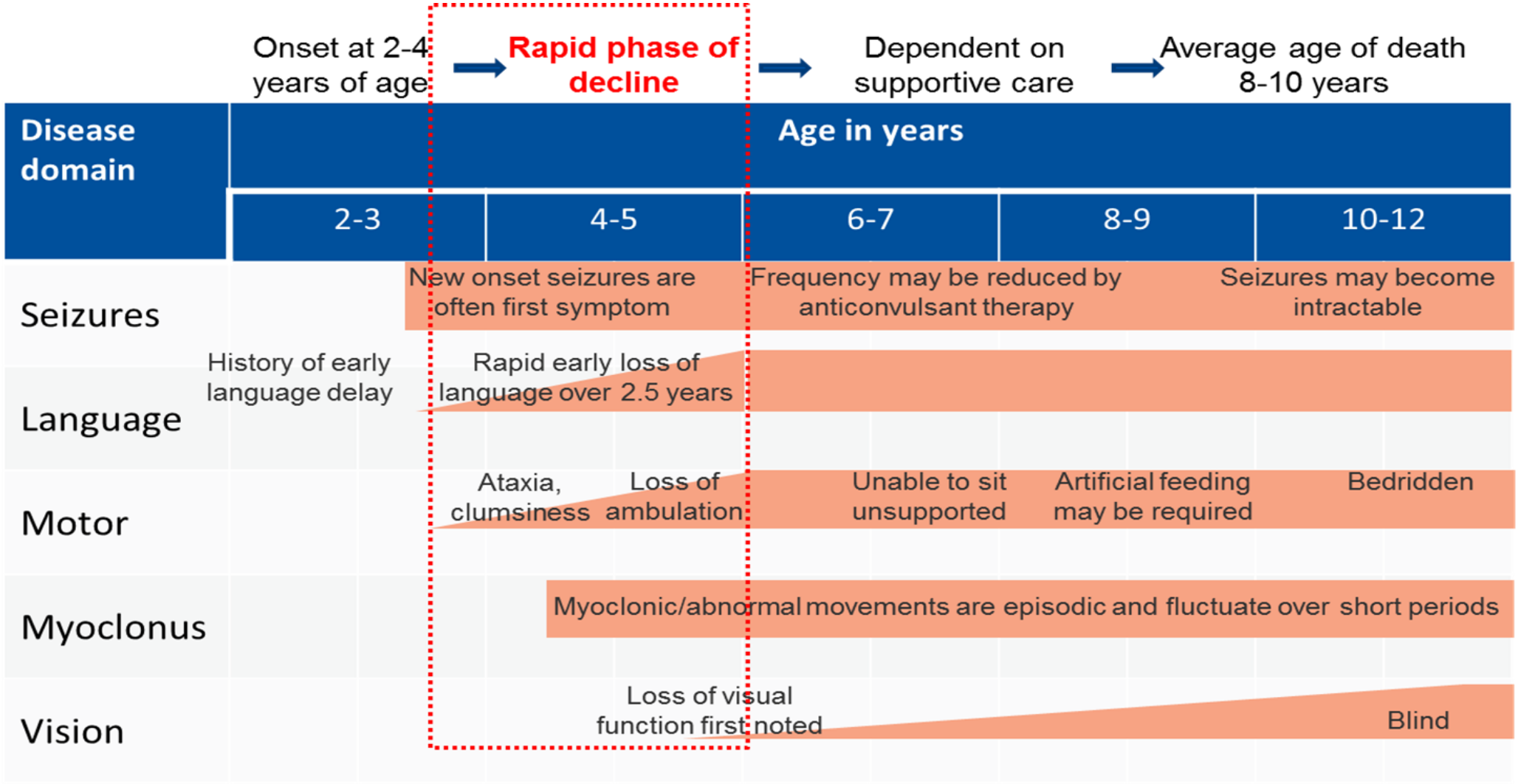
- Based on laboratory testing following clinical suspicion → Demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) and the identification of pathogenic variants in both alleles of the *TPP1/CLN2* gene

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: 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 Disease progression • CLN2 Clinical Rating Scale (reported as 4-domain scale and combined score of the motor and language domains) • Weill Cornell LINCL Scale (4-domain scale) • Hamburg scale	Majority of analyses based on disease progression, using CLN2 Clinical Rating Scale 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 • Need for medical care (including hospitalisation, emergency care and primary and secondary care appointments, and concomitant medication) • Mortality • Adverse effects of treatment (including immune response and effects and complications related to treatment administration) • 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. 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. No other differences from final scope.	• Acknowledges that not all the outcomes were collected in the included studies. • Company's approach of supplying data from other sources is reasonable. • 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. 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.

* See appendix – Comparison of baseline characteristics (1) (2)

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) 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)

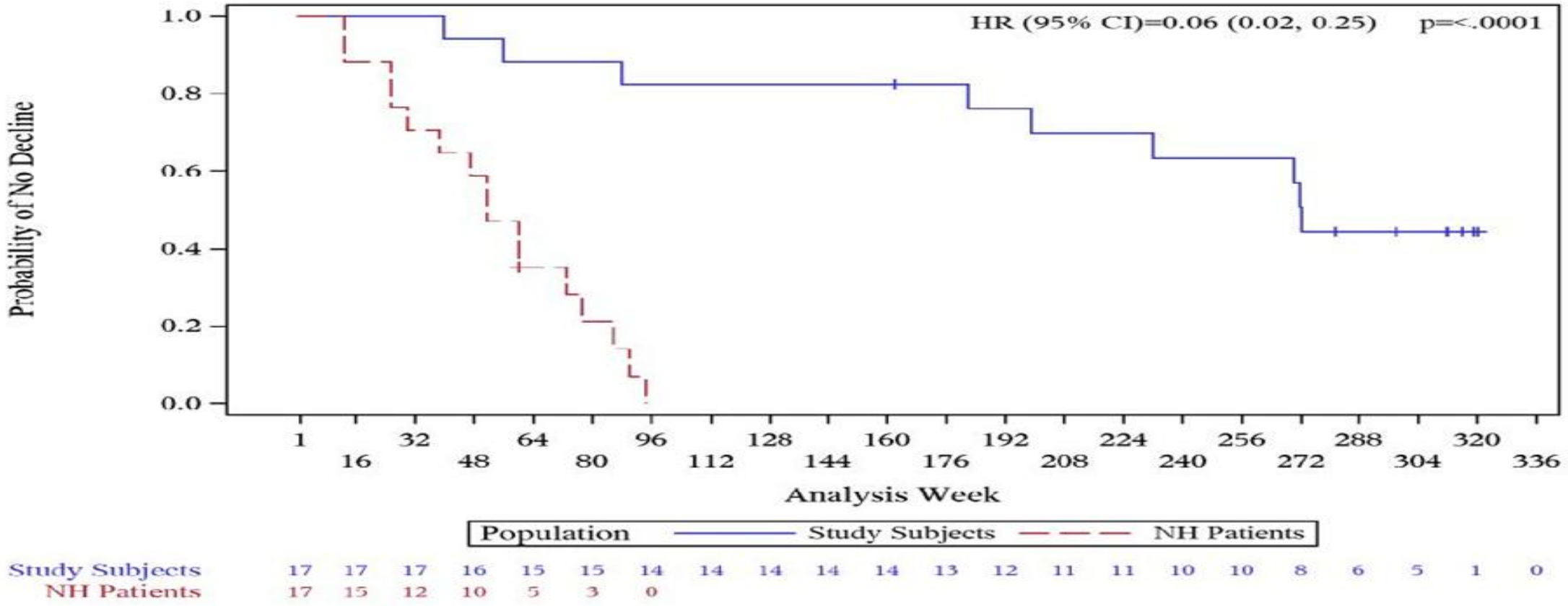
	NH and MAA FAS matched patients		NH and MAA new starter matched patients	
	NH (n=26)	MAA FAS (n=26)	NH (n=17)	MAA new starters (n=17)
Age at baseline (years)				
n	26	26	17	17
Mean (SD)	4.35 (1.11)	4.37 (1.07)	4.53 (1.18)	4.56 (1.10)
Median (Min, Max)	4.25 (1.75,8.75)	4.33 (1.72, 8.5)	4.25 (3.33, 8.75)	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



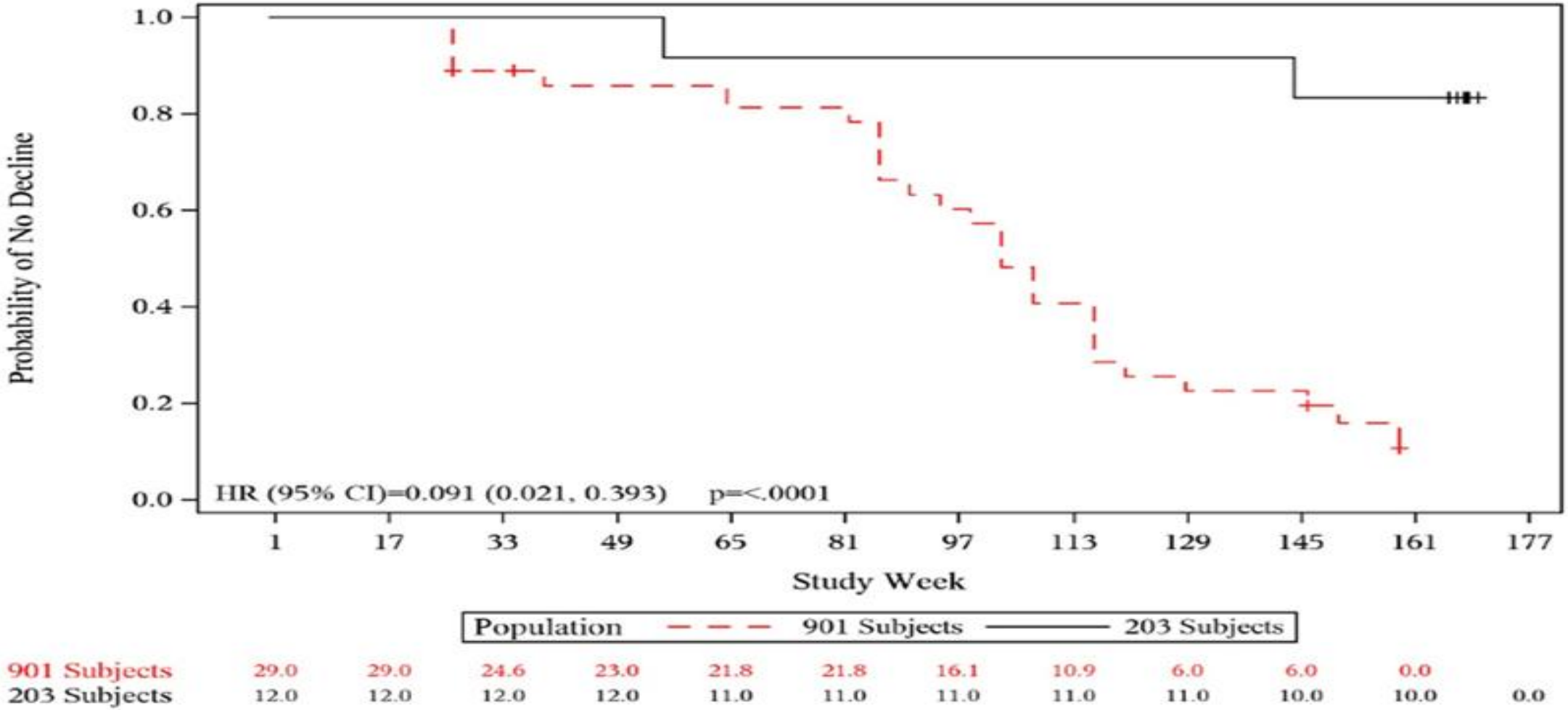
Link to – Clinical trials results

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)

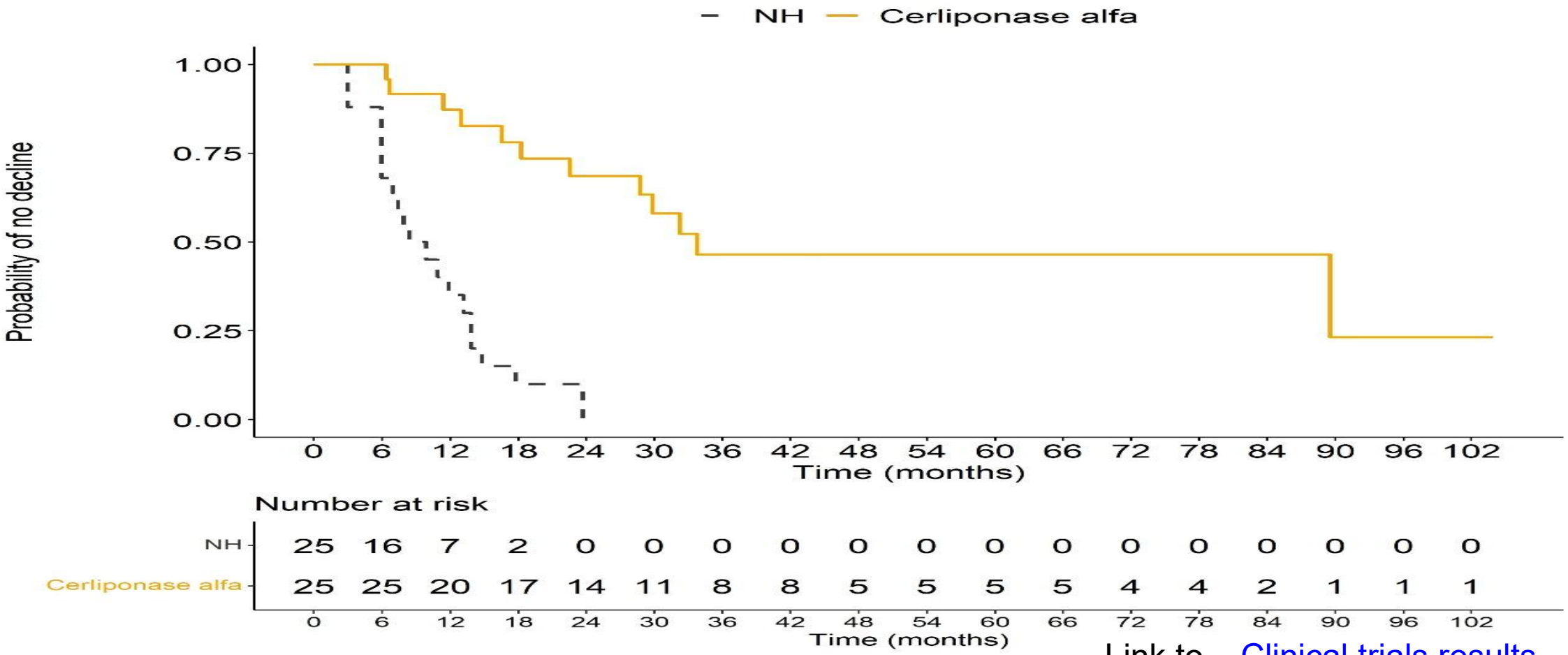


Abbreviations: ML, Motor and Language; NH, Natural history;

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)

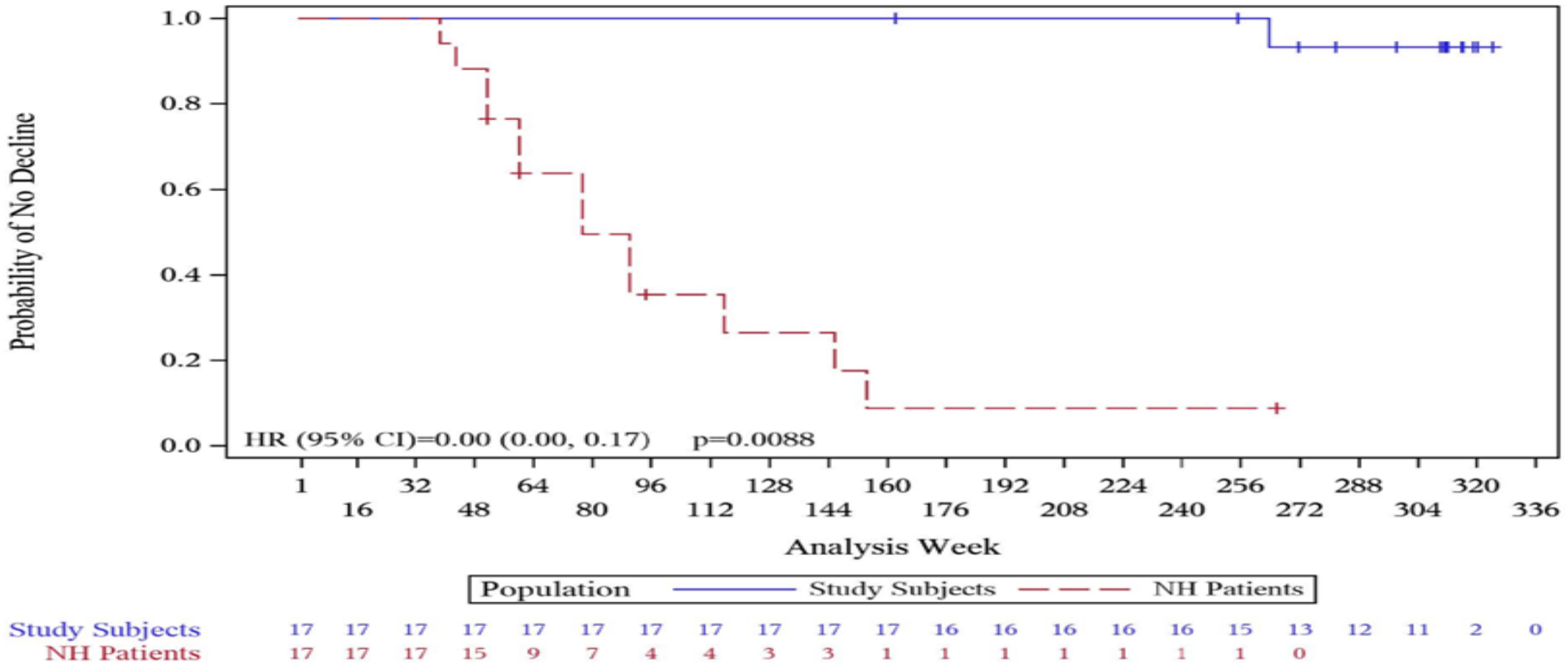


Link to – Clinical trials results

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)

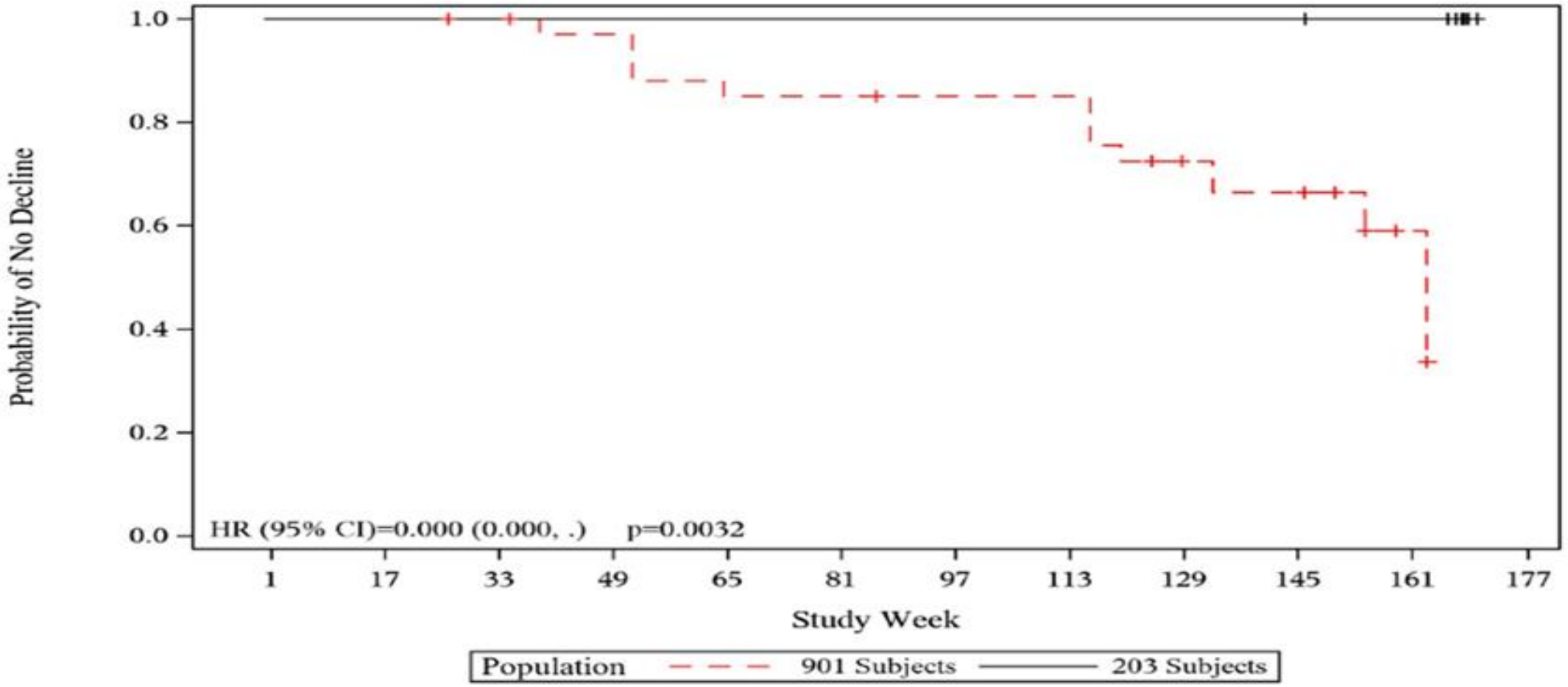


Link to – Clinical trials results

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)



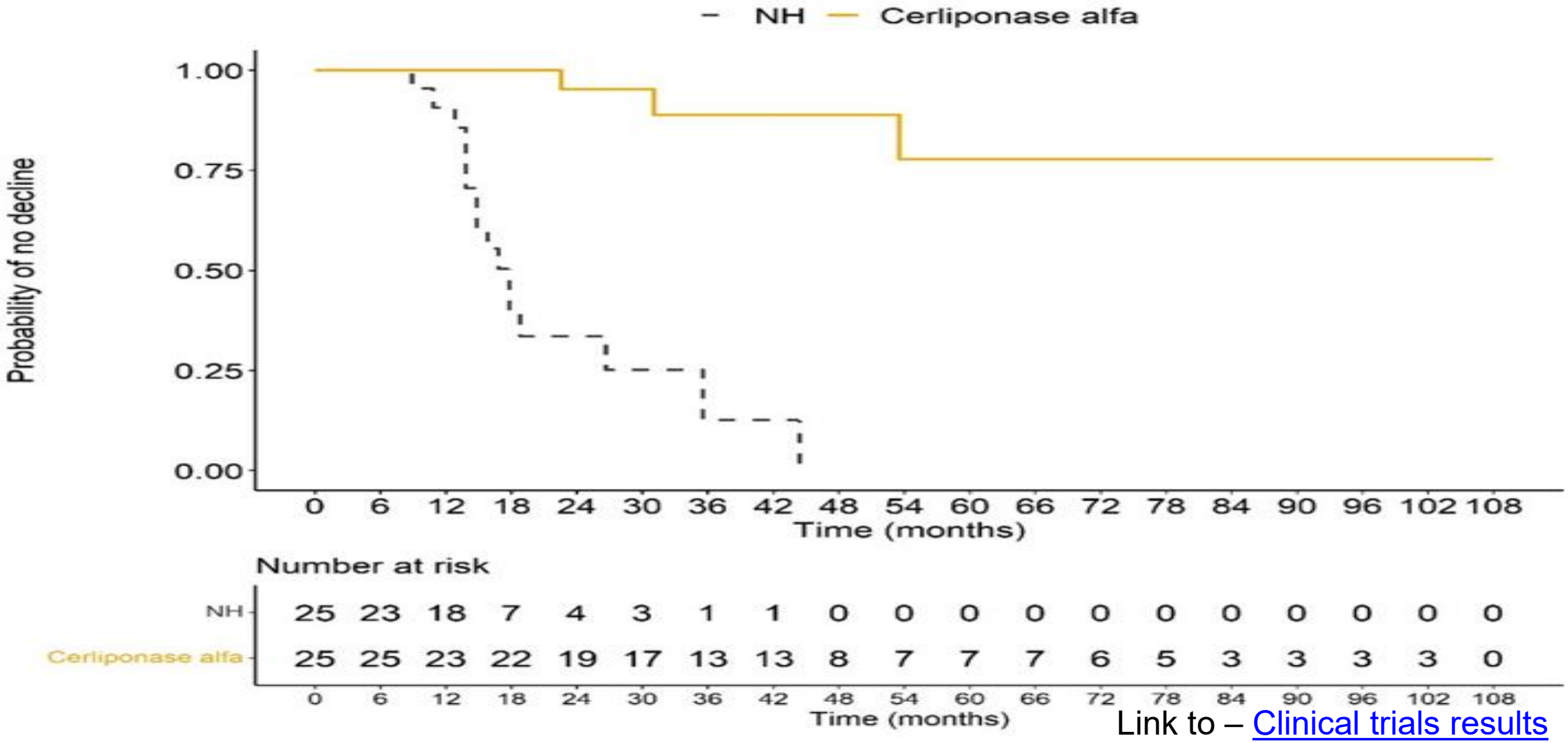
Link to – Clinical trials results

NICE

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)

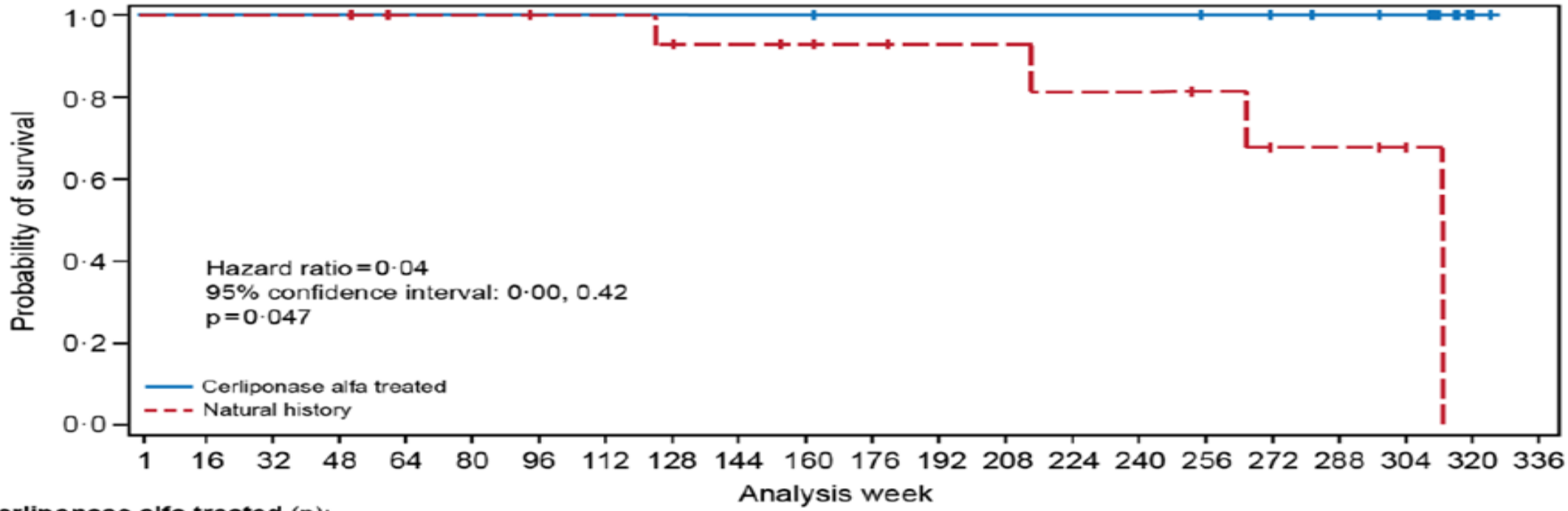


Link to – Clinical trials results

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 Ongoing end data: 2030	7th September 2017 – 31 weeks	26th April 2023 - 151 weeks 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;

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

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

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 • 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