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

For zoom – CON and DPD information redacted

Highly Specialized Technology Appraisal Committee [12 June 2024]

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Company: BioMarin Pharmaceuticals

Abbreviations: CON, Confidential; DPD, Depersonalised data;

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Appraisal recap

November 2019
MA Entry
(HST12)

- Cerliponase alfa received a positive recommendation by NICE 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 the following areas:
  - CLN2 Clinical Rating Scale scores over time and whether there was long-term stabilisation of disease
  - improvements over time in motor and language score at time of treatment initiation,
  - the frequency and severity of tonic-clonic seizures
  - myoclonus and dystonia control, impact on visual acuity (VA)
  - and measures of QoL

June 2024
MA-review

- This HST represents a new review of cerliponase alfa focusing on the existing and the new evidence generated since the previous HST
  - long-term effectiveness data from study 190-202 (which is an extension of study 190-201)
  - new sources of clinical effectiveness evidence from the MAA and from study 190-203
  - three long term safety studies
  - and two supplementary studies

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Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; HST, Highly specialised technology; MA, Managed access; MAA, Managed access agreement;

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;

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"

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Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2;

Equality

Clinical expert comments

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

Company comments

- 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)*

Innovation and other considerations

Company comments

- 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
- The positive impact of cerliponase alfa on the financial burden on families cannot be adequately captured in the reference case analysis
- The impact of CLN2 for unaffected siblings could only be naively estimated

Clinical expert comments

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

Lead team comments

- The generation study is a research study underway (in some hospitals in England)
  - ↳ May identify babies with this condition sooner (Study runs till March 2025)

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; HST, Highly specialised technology; MAA, Managed access agreement;

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 was granted on 30th May 2017 and UK marketing authorisation was granted on 1st 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: £20,107.00 per pack of cerliponase alfa (2x150 mg vials) • The recommended dosage for those >2 is 300mg every other week (annual cost £522,782) • Company proposed a confidential commercial arrangement which has not (yet) been approved by NHS England, and so not incorporated by NICE

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

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Key clinical trials*

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

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;

Clinical trial results

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

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			
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

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

The EAG has identified four clinical effectiveness key issues

↳ **However, because of a lack of evidence no alternative approaches were possible**

↳ **It is not anticipated that additional data will become available during the appraisal**

Uncertainty about trends in motor function and language

- Disease progression after long-term use of cerliponase alfa is currently unclear and so is the rate of progression in the most severe health states
- Rates of progression may vary across patients and within patients it is possible people could experience long periods of stability, or periods 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 be helping to 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
  - ↳ If cerliponase alfa extends life non-neurological outcomes may have a greater impact on HRQoL

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Abbreviations: HRQoL, Health related quality of life; QoL, Quality of life;

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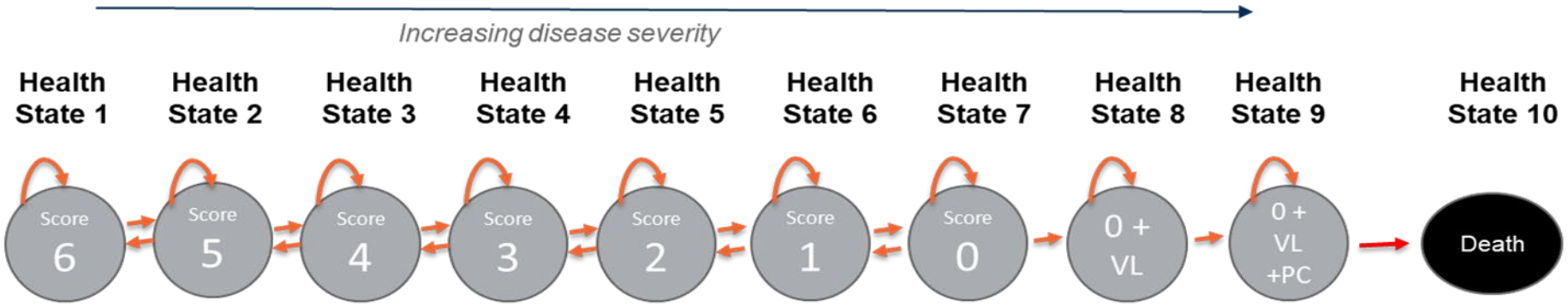
Cost effectiveness key issues

Issue	Resolved?	ICER impact
Uncertain structural link between disease progression on motor and language domains, and other progressive symptoms	No – for discussion	Unknown
Generalisability of company's preferred baseline distribution of patients across health states	No – for discussion	Large
Uncertainty around the initial stabilisation assumption	No – for discussion	Large
Appropriateness of evidence source informing transition probabilities in health states 1-7	No – for discussion	Large
Robustness of transition probability estimates in health states 1-7	No – for discussion	Unknown
Vision loss progression may not reflect natural history of disease	No – for discussion	Large
Cerliponase alfa treatment discontinuation	No – for discussion	Large
Uncertainty around treatment specific health state utilities	No – for discussion	Large

Abbreviations: ICER, Incremental cost-effectiveness ratio;

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;

Key issue: Link between disease progression on motor and language domains & progressive symptoms (1/2)

Company

- Models treatment effect using changes to the ML score and assumes changes in the ML score is linked to the proportion of individuals experiencing progressive symptoms
- Model assumes the proportion of individuals with progressive symptoms (distress, dystonia, myoclonus, feeding tube and musculoskeletal pain) in a given health state is lower in the cerliponase alfa arm
  - ↳ Estimates informed by clinical expert elicitation

EAG comments

- Company's approach to modelling a treatment effect links progression in terms of motor and language symptoms to other progressive symptoms → Uncertain but clinically plausible
- Association between disease progression on motor and language functions and other progressive symptoms as modelled was not as observed in the primary data
  - ↳ The company collected some, limited evidence on vision, tonic-clonic seizures, myoclonus, dystonia and requirement for feeding tube in its trials but does not discuss how this evidence supports the assumptions in the model
  - ↳ Committee in HST12 hoped data collection would reduce uncertainty around progressive symptoms
- Compared to HST12 company apply additional within health state treatment effect on resource use estimates → In HST12 only seizures were assumed to differ by treatment group

Abbreviations: HST, Highly specialised technology; ML, Motor and Language;

Key issue: Link between disease progression on motor and language domains & progressive symptoms (2/2)

EAG comments

- The effect of cerliponase alfa on progressive symptoms is modelled inconsistently between costs & HRQoL
  - ↳ Progressive symptom resource use by health state and treatment informed by elicited clinical opinion
  - ↳ HRQoL by health state and treatment is informed by vignettes that do not align with elicited estimates
- Clinical advice → Estimates of the proportion of individuals experiencing progressive symptoms in each health state / between treatment arms seemed clinically plausible
- **Scenario analyses:** Proportion of individuals with progressive symptoms (other than seizures) is the same in both treatment groups *(extreme/conservative scenario)*

* See appendix – Progressive symptoms by HS and arm

Would it be expected that the proportion of individuals with progressive symptoms (distress, dystonia, myoclonus, musculoskeletal pain and feeding tube requirement) in a given health state is lower for those people receiving cerliponase alfa?

Abbreviations: HRQoL, Health related quality of life; HS, Health state;

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

Company

- Starting age and baseline distribution informed by the subgroup of younger than 3 from Study 190-203
  - ↳ 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
- Clinical advice
  - ↳ There is still a lack of awareness of CLN2 amongst GPs and current clinical guidance indicate neurology referrals only after some motor and language function deterioration
  - ↳ *"newborn screening for CLN2 is conceivable within the next 5 years".*
- **Scenario analyses:** Based on the full population of Study 190-203, and new patients from the MAA

EAG comments

- Base case baseline characteristics are in line with committees' preferred approach in HST12, people initiating treatment are equally distributed between health states 1 & 2 (ML score 6 & 5, respectively)
- 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)

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

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

EAG comments

- 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
- It is uncertain if newborn screening for CLN2 will be routinely conducted in the near future
- **Scenario analyses:** Distributions suggested by clinical adviser

Clinical expert comments

- CE1: Provided data (age at diagnosis and ML Score) from a review of people treated at GOSH (n=19)

Abbreviations: CE, Clinical expert; CLN2, Neuronal ceroid lipofuscinosis type 2; GOSH, Great Ormond Street Hospital; HST, Highly specialised technology; MAA, Managed access agreement; ML, Motor and Language;

Key issue: Baseline distribution across health states (3/4)

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

Health State	ML Score	Company base case Study 190-203, <3 years (N=8)	Study 190-203 (N=14)	MAA new patients (N=24)	EAG base case Original HST12	EAG CE *"Current clinical practice"*	EAG CE *"Clinical practice in 5-year time"*	*CE submission (Review of patients treated at GOSH) (N=19)**
Age		2	-	-	4	4.5	*3.5*	*26.3% (N=5)** < 4 73.6% (N=14) Between 4 and 4 years 11 months*
1	**6**	87.5%	50.0%	18.2%	50%	15%	50%	10.5%
2	**5**	12.5%	7.1%	13.6%	50%	45%	35%	10.5%
3	**4**	0.0%	21.4%	45.5%	-	30%	12.5%	57.9%
4	**3**	0.0%	7.1%	13.6%	-	10%	2.5%	10.5%
5	**2**	0.0%	7.1%	9.1%	-	-	-	-
6	**1**	0.0%	7.1%	0.0%	-	-	-	-

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

Abbreviations: CE, Clinical expert; EAG, External assessment group; GOSH, Great Ormond Street Hospital; MAA, Managed access agreement; ML, Motor and Language;

Key issue: Baseline distribution across health states (4/4)

Clinical expert comments

- CE1: Suspects age at diagnosis will decrease slightly with better education
  - ↳ Only newborn screening would lead to a significant change in early diagnosis
- 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)

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

Abbreviations: CE, Clinical expert; ML, Motor and Language;

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

Company

- Assume 100% of people who enter the model in HS1 (ML score 6) are initial stabilisers
  - ↳ *Initial stabilisers: Remain in HS1 for the first 6 years. Beyond 6 years, transitions to worse health states occur at half the rate of the transition probabilities applied to those who enter the model in a worse health state.*
- 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
- **Scenario analyses:**
  - ↳ Reduction of transition probabilities for initial stabilisers by i) 75% and ii) 100% instead of 50%;
  - ↳ Initial stabilisation is assumed to persist for 12 instead of 6 years

EAG comments

- Base case assumes 80% of people who enter the model in HS1 (ML score 6) are initial stabilisers
- 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]

Abbreviations: CSR, Clinical study report; HS, Health state; ML, Motor and Language;

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

EAG comments

- 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
- 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
- Company only explore more optimistic stabilisation assumptions
- **Scenario analyses** → Reduction of transition probabilities for initial stabilisers by i) 25% and ii) 0%

Clinical expert comments

- 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

Are the company's initial stabilisation assumptions (% of people and reduction of transition probabilities) suitable for decision making?

Key Issue: Evidence informing transition probabilities (1/2)

Company

- Preferred evidence source is Study 190-203
  - ↳ Aligns with the starting population in its base case and population likely to receive cerliponase alfa in the near future
- SoC transition probabilities were estimated data from Study 190-901 matched to study 190-203
- 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
  - ↳ COVID 19 delayed diagnosis and treatment for some

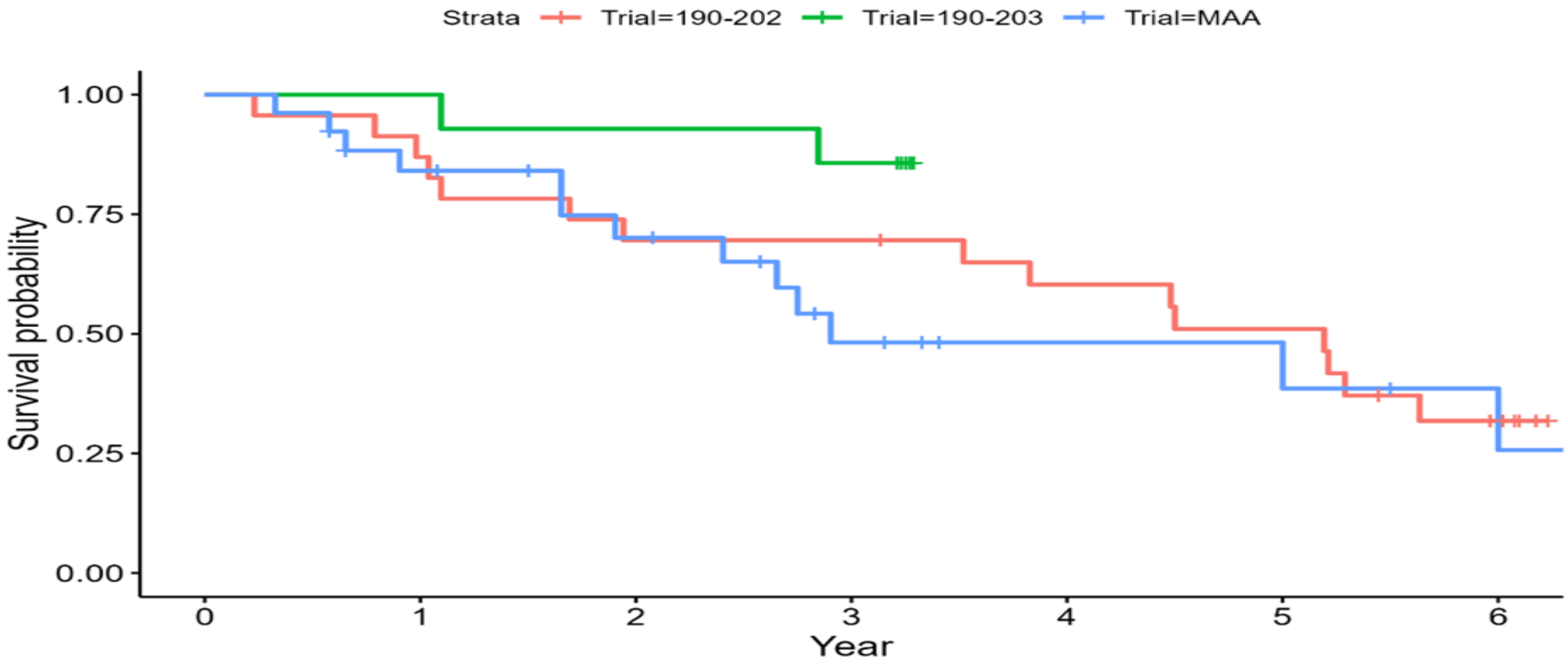
Scenario analyses:

- All patients from studies (i.e., study 190-203, study 190-201/202, and the MAA database) pooled and compared with one-to-one matched SoC patients from Study 190-901.
- All patients from the pooled studies, with separate transition probabilities for <6 months from baseline and ≥6 months from baseline for cerliponase alfa patients and Study 190-901 one-to-one matched patients for SoC. (Captures the impact of any delay in the full treatment effect of cerliponase alfa being realised)

Abbreviations: EAP, Expanded access program; MAA, Managed access agreement; SoC, Standard of care;

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: Evidence informing transition probabilities (2/2)

EAG comments

- 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 also introduce bias against cerliponase alfa 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.

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

Abbreviations: EAG, External assessment group; MAA, Managed access agreement; ML, Motor and Language;

Key Issue: Transition probability estimates

Company

- Chosen methodology accounts for → Multiple data sources with differing observation intervals, differing durations of follow-up and transitions that were intermittently observed in time

EAG comments

- Concerned estimates for the transition probabilities may not be robust
  - ↳ Small numbers of events were used to inform the transition probabilities
  - ↳ Unclear impact of arbitrary initial values and potential overfitting to the observed data
  - ↳ Clinical advice suggest that transitions to healthier health states seen in the trial may be temporary → Allowing backward transitions means that in the model people in the cerliponase alfa arm may transition to increasingly healthier HSs, which may be clinically implausible
  - ↳ The company's suggestion that using a multivariate normal distribution informed by a covariance variance matrix in the PSA results in nonsensical values brings into question the reliability of its estimation method
- The company did not test alternative estimation methods → Preferred approach would have been to investigate how other i) sets of initial values, ii) statistical approaches, and iii) level of health state aggregation, impacted derived transition probabilities and/or statistical model goodness of fit.
- **Scenario analyses** → Transitions to previous healthier HSs are not possible

- Is the company's approach to estimating transition probabilities suitable for decision making?
- Should the modelling allow backward transitions?

Abbreviations: EAG, External assessment group; HS, Health state; PSA, Probabilistic sensitivity analysis;

Key issue: Vision loss progression (1/2)

Company

- In both the cerliponase alfa and SoC arms vision loss is modelled by assuming:
  - ↳ Vision loss would affect all patients in health states 7-9
  - ↳ The proportion of patients with vision loss increases linearly from 0% at age 6 to 100% at age 20 in health states 1-6 → Informed by clinical opinion

EAG comments

- EAG's base case is in line with committees' preferred approach in HST12 and assumes cerliponase alfa has no impact on vision loss → Model assumes that the proportion of patients with vision loss in health states 1-6 is the same for individuals treated with cerliponase alfa and SoC
- The company's approach to modelling vision loss
  - ↳ May underestimate disutility associated with vision loss particularly in the cerliponase alfa arm as there will be a higher proportion of these patients alive and/or in health states up to health state 6 over time compared with SoC
  - ↳ Implies some delay to vision loss compared to SoC, as some patients in the SoC arm will reach health state 7 before they are 6 years old
- Clinical advice suggests → for most patients with CLN2 vision loss starts around 5 and with complete loss of vision by the time they reach 10 years old.
- **Scenario analyses** → Linear decline in vision loss with age between 6 and 10 years old

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; EAG, External assessment group; HST, Highly specialised technology; SoC, Standard of care;

Key issue: Vision loss progression (2/2)

Clinical expert comments

- CE1: The speed of vision loss varies between patients; some have reduced vision by 5.5 years of age while some have reasonable vision at 9 years of age
  - ↳ Suspects most patients will have functional vision loss by 6 years of age
- CE2: Vision loss usually begins between 5 & 6 years of age and many lose vision by 7-9 years of age (some may still perceive shadows and lights and large objects)
- Cerliponase alfa will only improve vision loss in all children if delivered via intravitreal injections

Which approach should be used to model vision loss progression?

Abbreviations: CE, Clinical expert;

Key issue: Treatment discontinuation rule (1/2)

Company

- Assume cerliponase alfa is discontinued once the individual enters HS 6 (ML score of 1)
- Cerliponase alfa would be unlikely to improve motor and language function after HS 6
- Scenario analysis → Discontinue in HS 7 and No discontinuation

EAG comments

- EAG's base case assumes discontinuation at HS 7 in line with committees' preferred approach in HST12
- The company's model
  - ↳ Allows transitions from HS 6 to less severe health states, which means that in the model people can transition from HS 6 to HS 5 and restart treatment which is unlikely in clinical practice
  - ↳ Maintains some of the treatment effect of cerliponase alfa post discontinuation because the transition probabilities only switch to the SoC transition probabilities at health state 7
  - ↳ Predicts that people will remain in HS 6 for 3.2 years on average
- It was not possible to implement into the model the stopping criteria in the MAA and clinical studies
- Clinical advice suggests
  - ↳ A treatment effect may remain for between 6-9 months post discontinuation, but you would not expect someone to remain in HS 6 for 3 years without treatment
  - ↳ In clinical practice stopping criteria would depend heavily on family preferences

Abbreviations: EAG, External assessment group; HS, Health state; HST, Highly specialised technology; MAA, Managed access agreement; SoC, Standard of care;

Key issue: Treatment discontinuation rule (2/2)

Clinical expert comments

- CE1: Decision to discontinue treatment would be made after considering the balance of pros and cons and the family's perception of QoL
  - ↳ Likely that treatment brings some benefits even to patients with significantly progressed disease, but this perception is not the same for all families
- ↳ CE2: Would expect treatment to be discontinued when ML scores reach 0-1 (HS 7-6) and would expect some treatment effect to potentially remain for months after discontinuation.
  - ↳ Due to the MAA and family assessment of QoL treatment discontinuation when ML scores reach 0-1 has been more challenging than anticipated.

- In what health state would people discontinue cerliponase alfa?
- Are the HST12 MAA starting and stopping criteria still appropriate?

* See appendix - MAA starting and stopping criteria

Abbreviations: CE, Clinical expert; HS, Health state; MAA, Managed access agreement; ML, Motor and Language; QoL, Quality of life;

* See – Health state utility values

Key issue: Treatment specific health state utilities (1/2)

Company

- Base case uses utilities elicited from 8 clinical experts in a vignette-based study (Gissen et al. (2021) → Health state specific utilities were conditional on treatment received
- **Scenario analyses**
  - ↳ Cerliponase alfa: Utilities derived from the MAA data (collected from family caregivers as proxies)
    SoC: Based on cerlioponase alfa MAA utilities and SoC utilities from Gissen et al. (2021)
  - ↳ Treatment-independent utility values → i) Gissen et al (2021) ii) MAA

EAG comments

- Base case uses utilities from the Gissen et al (2021) study despite considerable uncertainty
- Clinical advice suggests → Patients receiving cerliponase alfa experience fewer symptoms than those receiving SoC even if they have the same ML score
- Validation of vignettes may be biased as it was done by a single clinical expert who also participated in the Gissen et al. (2021) study
- The Gissen et al. (2021) study used clinical experts rather than carers as proxies (non-reference case method) this may not accurately reflect patients' quality of life
- Comparing cerliponase alfa and SoC utility values shows that the difference is substantial for HSs 5-9
- Clinical advice suggests → Significant drop in utility between HS 4 and HS 5 is expected due to a decline in mobility, but a similar decline was not seen in the cerliponase alfa utilities as would be expected
  - ↳ Observed inconsistencies indicate that applying treatment specific utility values may not correctly reflect the difference in HRQoL

* See – Health state utility values

Key issue: Treatment specific health state utilities (2/2)

EAG comments

- A different structural approach could have been applied that modelled the impact of progressive symptoms by assigning the symptom-related disutility to the proportion of patients experiencing these specific symptoms at each health state by treatment group
  - ↳ This analyses was not performed as it would require substantial structural changes and the identification of additional data

MAA informed scenario analyses

- The MAA data used family carers as proxies, but this data may be biased because continuation in the MAA was conditional on their being maintenance of HRQoL
- Using the MAA data leads to combining different sources, retains the issues regarding the robustness of Gissen et al., 2021, and further increases the uncertainty
- The company's approach also makes limited use of comparative evidence in Gissen et al. 2021
  - ↳ An alternative approach would be to estimate MAA SoC health utilities by estimating the utility difference between cerliponase alfa and SoC in Gissen et al., 2021 for each health state, and then applying it to the cerliponase alfa MAA health state utilities to estimate SoC MAA.
  - ↳ This alternative approach leads to generally higher utility estimates for SoC

Abbreviations: EAG, External assessment group; HRQoL, Health related quality of life; MAA, Managed access agreement; SoC, Standard of care;

Health state utilities

Table: Base-case health state utility values, Gissen et al, 2021 (Weighted average)

Health State	Cerliponase alfa	SoC
1	0.974	0.986
2	0.761	0.728
3	0.627	0.527
4	0.394	0.276
5	0.330	0.067
6	0.197	0.043
7	-0.115	-0.333
8	-0.176	-0.326
9	-0.197	-0.359

Table: Scenario health state utility values, MAA (Weighted average)

Health State	Cerliponase alfa	SoC	EAG's alternative for SoC
1	0.862	0.873	0.873
2	0.647	0.616	0.615
3	0.664	0.415	0.564
4	0.535	0.164	0.417
5	0.411	-0.045	0.149
6	0.276	-0.070	0.121
7	0.050	-0.445	-0.169
8	-0.012	-0.438	-0.161
9	-0.032	-0.471	-0.194

Which data source / approach should be used to obtain health state utilities?

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Abbreviations: EAG, External assessment group; MAA, Managed access agreement; SoC, Standard of care;

Company and EAG base case assumptions (1/2)

Table: Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Link between disease progression on motor and language domains, and other progressive symptoms	Link progression in terms of motor and language symptoms to other progressive symptoms Assume treatment effect on the proportion of patients incurring the costs of progressive symptoms	
Baseline distribution	HS1: 87.5%, HS2: 12.5%; age 2 years	HS1: 50%, HS2: 50%
Initial stabilisation	100% of patients in HS1 at model entrance are initial stabilisers	80% of patients in HS1 at model entrance are initial stabilisers
Evidence informing transition probabilities HSs 1-7	Study 190-203	'All patients' pooled dataset
Robustness of transition probability estimates in health states 1-7	Use the same estimation method	

Abbreviations: EAG, External assessment group; HS, Health state;

Company and EAG base case assumptions (2/2)

Table: Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Vision loss	Linear decline with age between 6 and 20 years old	Cerliponase alfa has no impact on progression to vision loss
Treatment discontinuation	In health state 6	In health state 7
Health state utilities	Gissen et al., 2021	
ECG monitoring costs	Excluded	Included
Neuro-disability mortality	Excluded	Included for health states 6-9
Psychiatric/behavioural support costs	Excluded	Included

Abbreviations: EAG, External assessment group; ECG, Electrocardiogram;

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.

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/be assigned 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;

The company and NHS England have not yet agreed a commercial arrangement, so the analyses presented considers the list price only

- **The ICERs from the company and EAG base cases as well as those from all the scenario analyses are substantially above the threshold NICE considers as an effective use of resources**

All CoE thresholds presented are based on undiscounted QALY gains excluding carer or sibling disutilities

Company base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	CoE threshold (£/QALY)
SoC	[redacted]	-0.28	-	-	-	
Cerliponase alfa	[redacted]	17.07	[redacted]	17.35	[redacted]	£300,000

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	CoE threshold (£/QALY)
SoC	[redacted]	-0.14	-	-	-	
Cerliponase alfa	[redacted]	17.50	[redacted]	17.64	[redacted]	£300,000

*When carer and sibling disutilities are included the company base case threshold is unchanged

Abbreviations: CoE, Cost effectiveness; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SoC, Standard of care;

EAG base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	CoE threshold (£/QALY)*
SoC	[redacted]	-0.68				
Cerliponase alfa	[redacted]	9.23	[redacted]	9.91	[redacted]	£168,899

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	CoE threshold (£/QALY)
SoC	[redacted]	-0.69				
Cerliponase alfa	[redacted]	9.26	[redacted]	9.94	[redacted]	Exact figure not stated but <£200K

Abbreviations: CoE, Cost effectiveness; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SoC, Standard of care;

EAG's preferred assumptions deterministic (1/2)

Table: EAG cumulative scenario analyses (deterministic)

Analysis	Assumption		Costs	QALYs	Inc cost	Inc QALYs	Cumulative ICER	CoE Threshold
1	Company's base case	SoC	[redacted]	-0.28	-	-	-	-
		CA	[redacted]	17.07	[redacted]	17.35	[redacted]	£300,000
2	1 + Baseline characteristics as per original HST12	SoC	[redacted]	-0.59		-		-
		CA	[redacted]	13.25	[redacted]	13.84	[redacted]	£266,658
3	2 + 80% of patients in HS1 are initial stabilisers	SoC	[redacted]	-0.59		-		-
		CA	[redacted]	12.64	[redacted]	13.23	[redacted]	£249,127
4	3 + Transition probabilities health state 1-7 informed by 'all patient dataset'	SoC	[redacted]	-0.72		-		-
		CA	[redacted]	8.82	[redacted]	9.54	[redacted]	£150,524

Abbreviations: CA, Cerliponase alfa; CoE, Cost effectiveness; EAG, External assessment group; HST, Highly specialised technology; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SoC, Standard of care;

EAG's preferred assumptions deterministic (2/2)

Table: EAG cumulative scenario analyses (deterministic)

Analysis	Assumption		Costs	QALYs	Inc cost	Inc QALYs	Cumulative ICER	CoE Threshold
5	4 + Vision loss as per HST12	SoC	[redacted]	-0.68	-	-	-	-
		CA	[redacted]	8.33	[redacted]	9.01	[redacted]	£143,946
6	5 + Neuro-disability mortality applies to HS1-9	SoC	[redacted]	-0.68		-		-
		CA	[redacted]	8.32	[redacted]	9.00	[redacted]	£142,751
7	6 + Treatment discontinuation at HS7	SoC	[redacted]	-0.68		-		-
		CA	[redacted]	9.23	[redacted]	9.91	[redacted]	£168,899
8	7 + Including ECG costs	SoC	[redacted]	-0.68		-		-
		CA	[redacted]	9.23	[redacted]	9.91	[redacted]	£168,899
EAG Base case	8 + Including psychiatric/behavioural support costs	SoC	[redacted]	-0.68		-		-
		CA	[redacted]	9.23	[redacted]	9.91	[redacted]	£168,899

Abbreviations: CA, Cerliponase alfa; CoE, Cost effectiveness; EAG, External assessment group; ECG, Electrocardiogram; HS, Health state; HST, Highly specialised technology; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SoC, Standard of care;

Key issue scenario analyses – Applied to company base case (1/3)

Table: Scenario analyses (deterministic)

Key Issue	Scenarios
Link between disease progression on motor and language domains, and other progressive symptoms	Proportion of patients with progressive symptoms (other than seizures) is the same in both treatment group as elicited from company's clinical experts for CA
	Proportion of patients with progressive symptoms (other than seizures) is the same in both treatment group as from company's clinical experts for SoC
Baseline distribution across health states	Clinical expert estimate of current clinical practice
	Clinical expert estimate of clinical practice in 5-years time
	As per original HST12
	Study 190-203 starting distribution MAA (new patients) starting distribution:
Uncertainty around the initial stabilisation	80% of patients in HS1 at model entrance are initial stabilisers
	100% progression multiplier for initial stabilisers
	75% progression multiplier for initial stabilisers
	Duration of ML 6 stabilisation: 12 years
	Reduction in transition probabilities (ML 6 stabilisers): 75%
	Reduction in transition probabilities (ML 6 stabilisers): 100%
Evidence informing transition probabilities	Source of transitions: All patients
	Source of transitions: All patients (piecewise at 6 months)

Abbreviations: CoE, Cost effectiveness; EAG, External assessment group; ECG, Electrocardiogram; HS, Health state; HST, Highly specialised technology; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SoC, Standard of care;

Key issue scenario analyses – Applied to company base case (2/3)

Table: Scenario analyses (deterministic)

Key Issue	Scenarios
Transition probability estimates	Backwards transitions to healthier states not allowed
Vision loss progression	Linear decline with age between 6 and 10 years old
	As per original HST12 (driven by cumulative proportion of vision loss in the SoC)
Treatment discontinuation rule	Treatment discontinuation at HS7
	No treatment discontinuation
Treatment specific health state utilities	Utilities informed by MAA for cerliponase alfa; SoC health state utilities calculated by assuming the same change in utilities between health states for those treated with SoC in Gissen et al., 2021
	Utilities informed by MAA for cerliponase alfa; SoC health state utilities calculated by assuming the same difference in utilities between treatments at each health state as in Gissen et al., 2021.
	Source of utility values: MAA
	Gissen 2021, treatment-independent utility values
	MAA (all patients), treatment-independent utility values
ECG monitoring costs	Including ECG monitoring costs

Abbreviations: ECG, Electrocardiogram; HS, Health state; HST, Highly specialised technology; MAA, Managed access agreement; SoC, Standard of care;

Key issue scenario analyses – Applied to company base case (3/3)

Table: Scenario analyses (deterministic)

Key Issue	Scenarios
Carer and sibling disutilities	Carer and sibling disutilities for cerliponase alfa are the same as for the SoC values
	Carer and sibling disutilities for cerliponase alfa correspond to 75% of the SoC values

 Abbreviations: SoC, Standard of care;

Cost effectiveness key issues

Issue	Resolved?	ICER impact
Uncertain structural link between disease progression on motor and language domains, and other progressive symptoms	No – for discussion	Unknown
Generalisability of company's preferred baseline distribution of patients across health states	No – for discussion	Large
Uncertainty around the initial stabilisation assumption	No – for discussion	Large
Appropriateness of evidence source informing transition probabilities in health states 1-7	No – for discussion	Large
Robustness of transition probability estimates in health states 1-7	No – for discussion	Unknown
Vision loss progression may not reflect natural history of disease	No – for discussion	Large
Cerliponase alfa treatment discontinuation	No – for discussion	Large
Uncertainty around treatment specific health state utilities	No – for discussion	Large

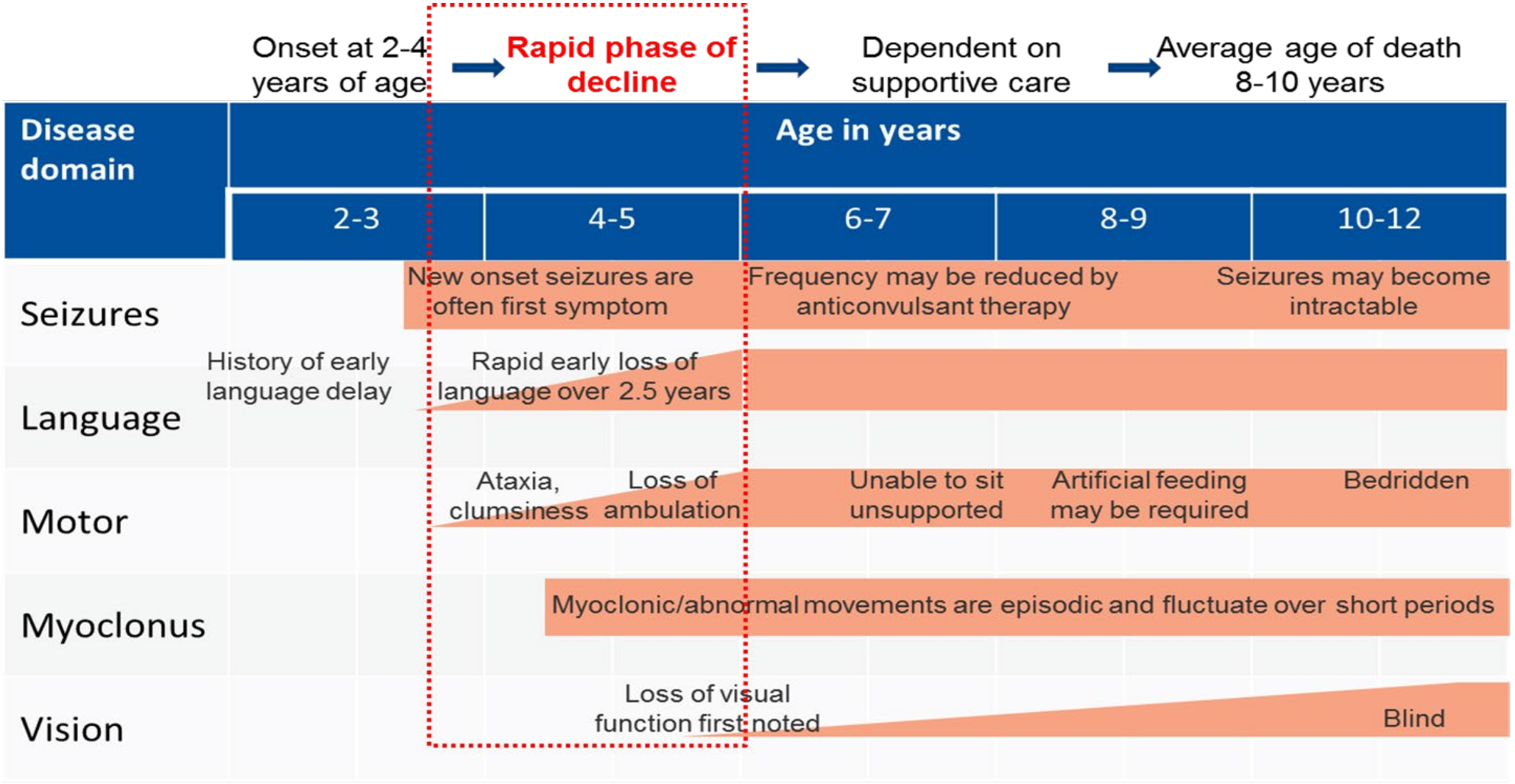
Abbreviations: ICER, Incremental cost-effectiveness ratio;

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

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

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.

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		??
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;

Progressive symptoms by HS and arm

Table: Comparison of proportion of individual with progressive symptoms in the original HST and the company's economic model

Health state	ML score	Distress			Dystonia			Myoclonus			Feeding tube			Musculoskeletal pain	
		HST12	CEM		HST12	CEM		HST12	CEM		HST12	CEM		CEM	
			CA	SoC		CA	SoC		CA	SoC		CA	SoC	CA	SoC
1	6	3%	2%	5%	0%	0%	0%	3%	0%	20%	0%	0%	0%	5%	5%
2	5	9%	5%	19%	15%	0%	10%*	25%	0%	40%	89%	0%	10%	10%	20%
3	4	30%	10%	20%	15%	20%	40%	50%	20%	70%	100%	0%	50%	15%	30%
4	3	39%	20%	30%	30%	40%	80%	98%	40%	90%	100%	0%	70%	30%	50%
5	2	48%	30%	40%	60%	50%	100%	100%	50%	100%	100%	20%	100%	40%	60%
6	1	51%	40%	50%	73%	100%	100%	100%	100%	100%	100%	80%	100%	60%	80%
7	0	54%	50%	60%	63%	100%	100%	100%	100%	100%	100%	100%	100%	80%	90%
8		56%	70%	70%	63%	100%	100%	100%	100%	100%	100%	100%	100%	80%	90%
9		56%	70%	70%	63%	100%	100%	100%	100%	100%	100%	100%	100%	80%	90%

Link to - Link between disease progression on motor and language domains & progressive symptoms (2/2)

 Abbreviations: CA, Cerliponase alfa; CEM, Company economic model; HST, Highly specialised technology; ML, Motor and Language; SoC, Standard of care;

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)

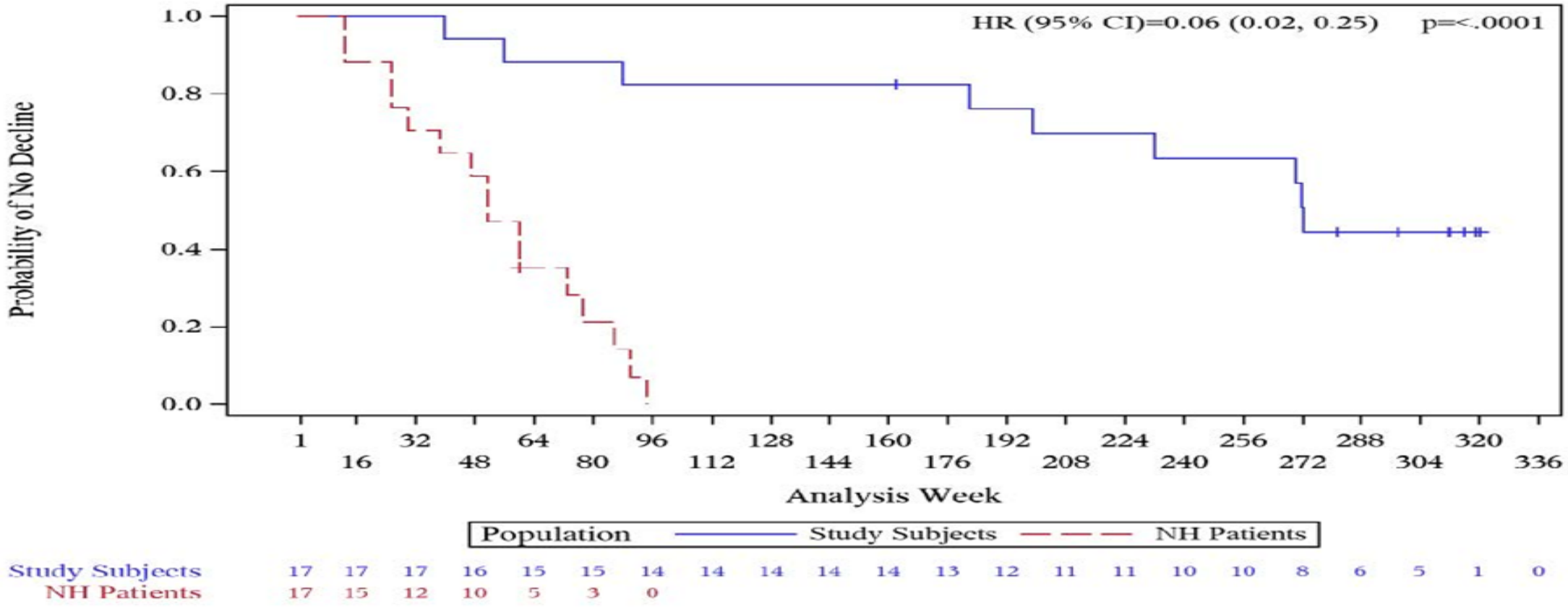
	NH and MAA FAS matched patients		NH and MAA new starter matched patients	
	NH (n=26)	MAA FAS (n=26)	NH (n=17)	MAA new starters (n=17)
Age at baseline (years)				
n	26	26	17	17
Mean (SD)	4.35 (1.11)	4.37 (1.07)	4.53 (1.18)	4.56 (1.10)
Median (Min, Max)	4.25 (1.75,8.75)	4.33 (1.72, 8.5)	4.25 (3.33, 8.75)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



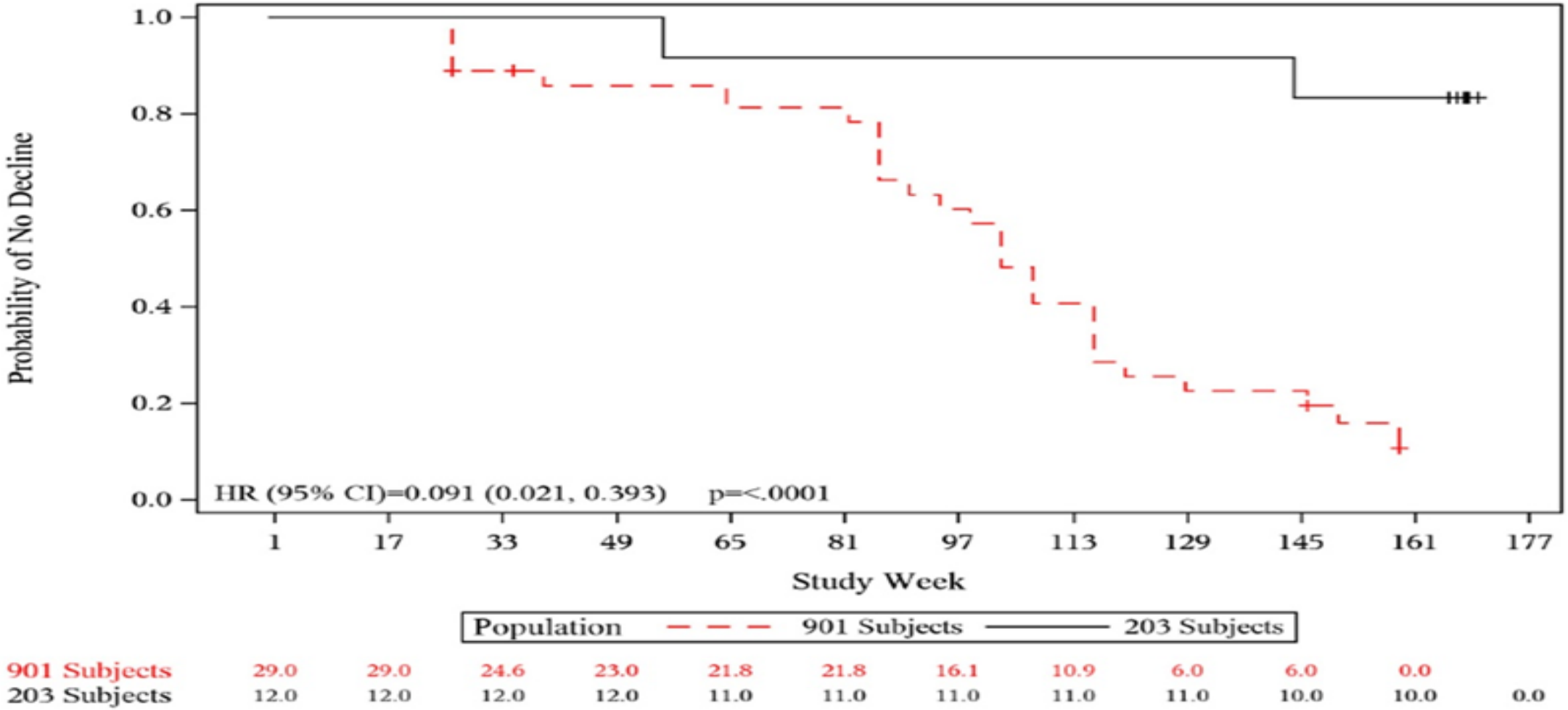
Link to – Clinical trials results

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)

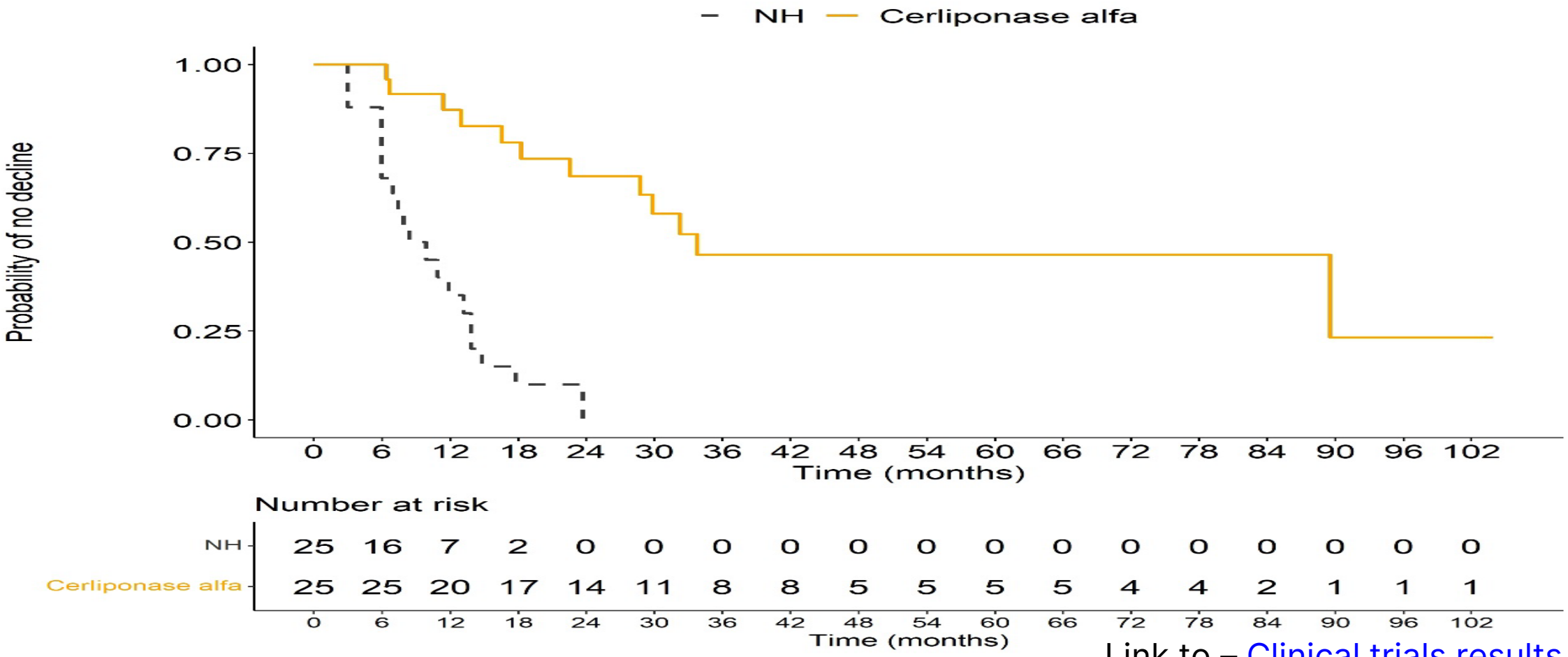


Abbreviations: ML, Motor and Language; NH, Natural history;

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)

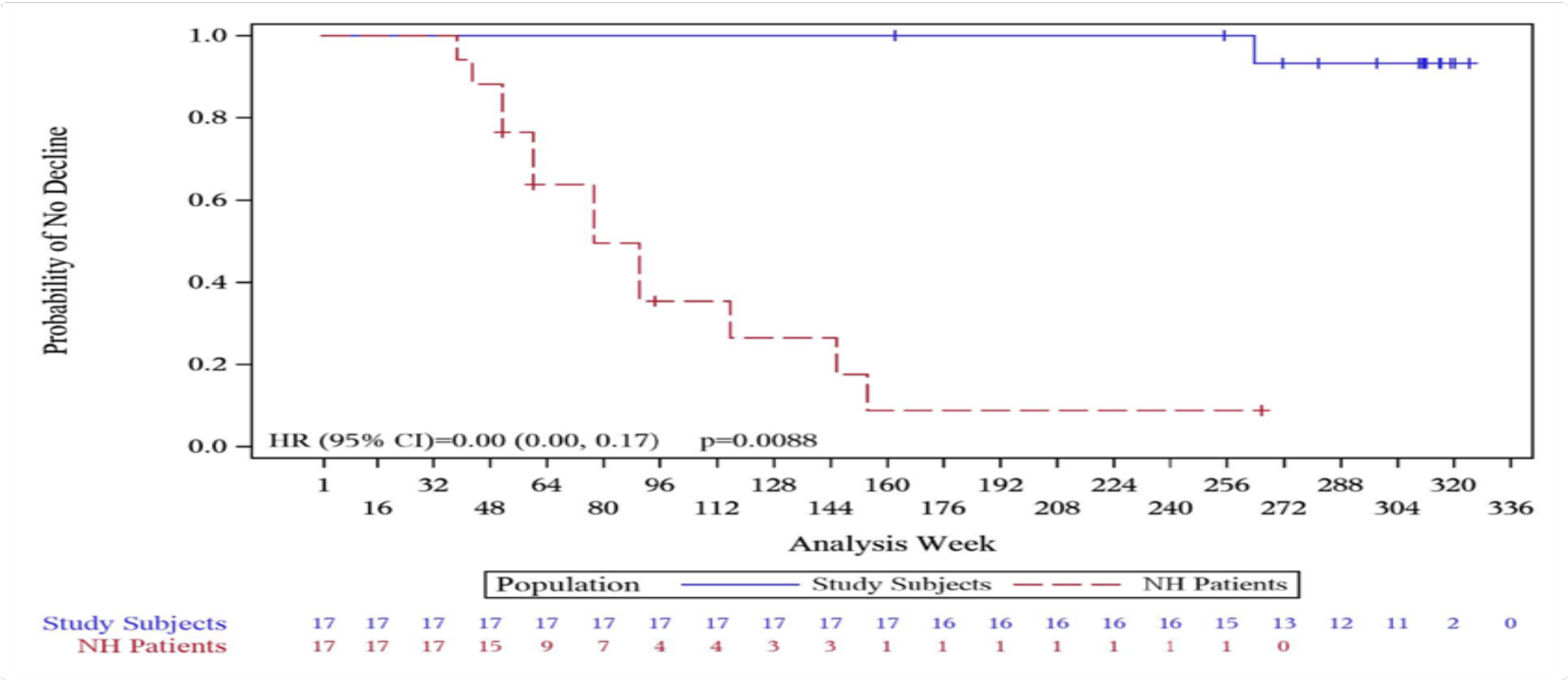


Link to – Clinical trials results

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)



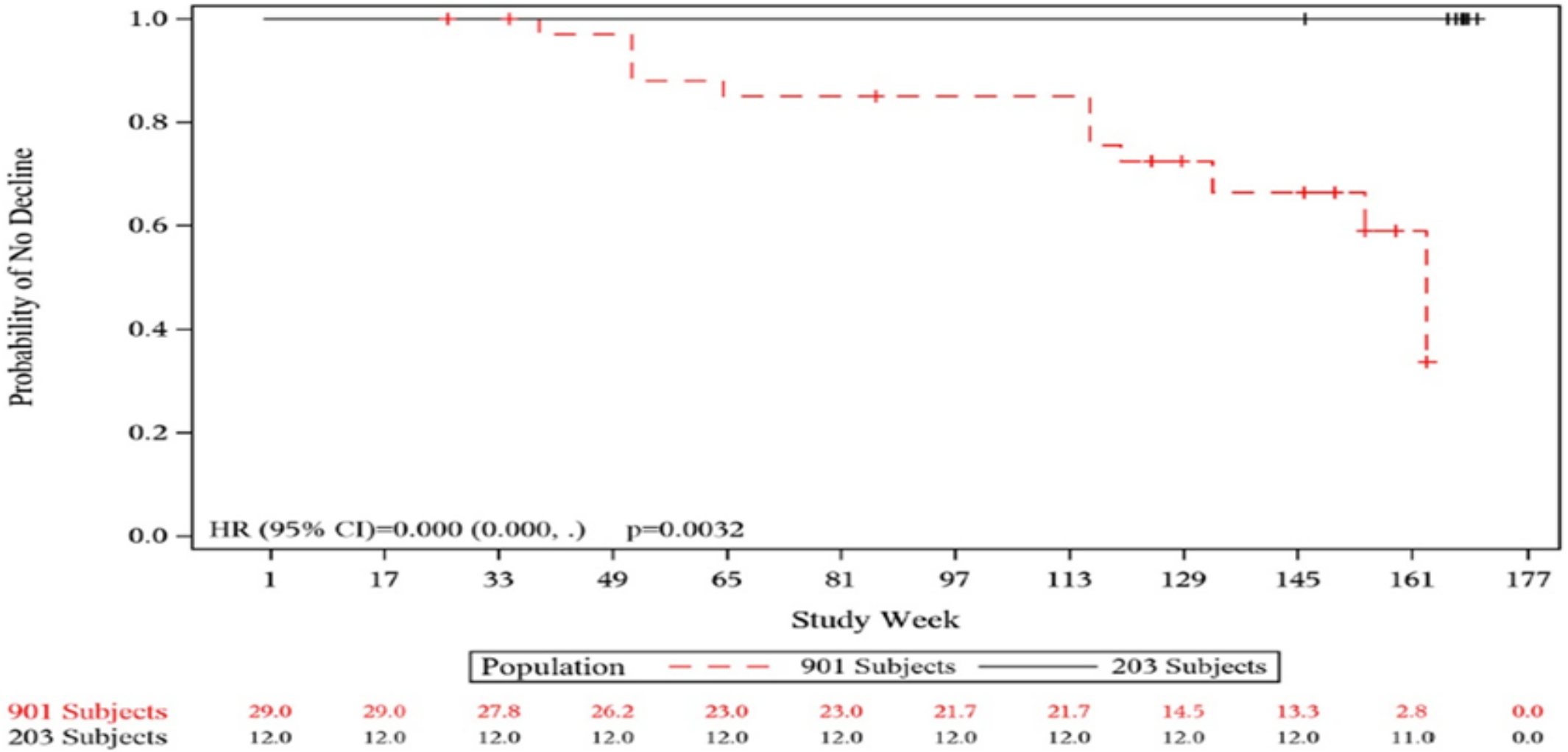
Link to – Clinical trials results

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)



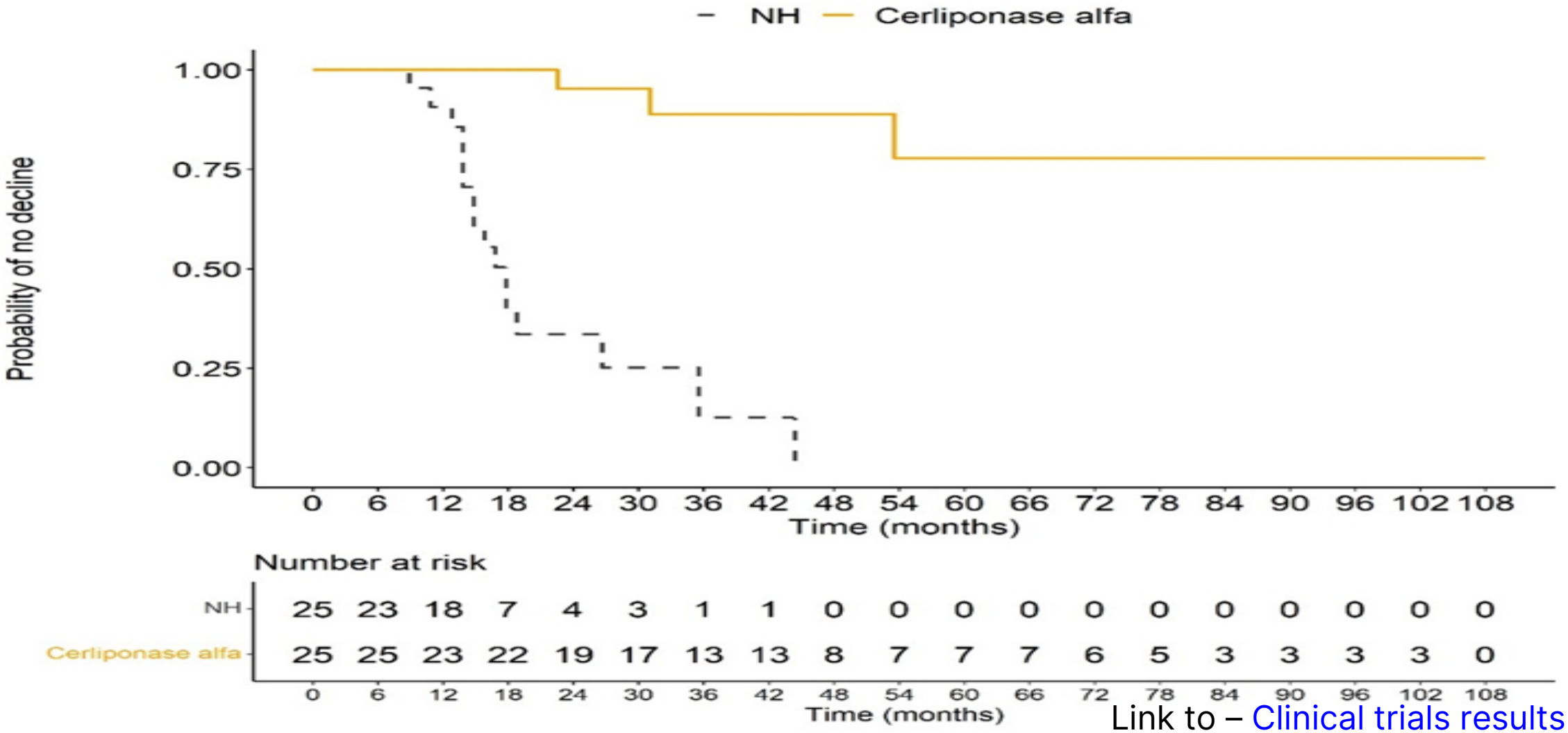
Link to – Clinical trials results

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)

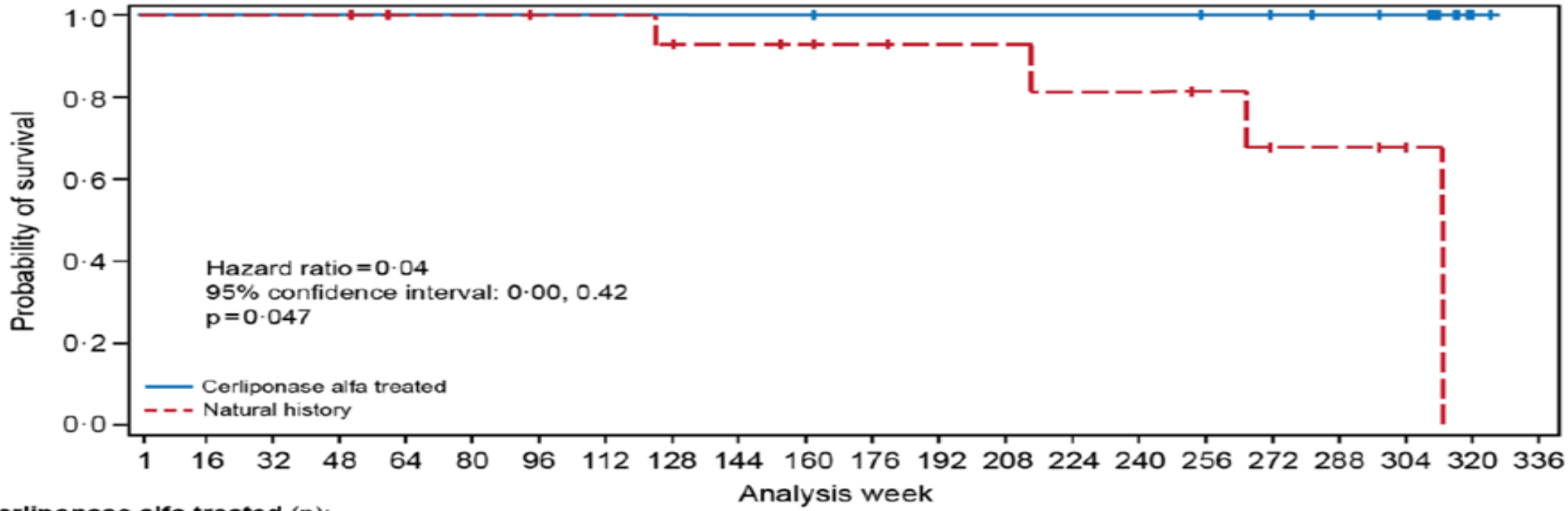


Link to – Clinical trials results

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;

MAA starting and stopping criteria (1/3)

Link to – Treatment discontinuation rule

5.8 Starting criteria for NEW patients

All of the following criteria must be met before treatment can be started:

- All patients must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity test.
- The patient is not diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit, e.g. cancer or multiple sclerosis.
- The patient has a CLN2 Rating Scale ML Score of 2 or above.
- A complete set of baseline assessments to confirm eligibility will be performed and recorded in the patient's clinical notes at the time of the first infusion. For patients who start receiving cerliponase alfa before the age of 3 years, the baseline assessment will be the first assessment conducted after their third birthday and conducted within 6 months of their third birthday

5.9 Stopping criteria applicable to all patients (including children under the age of 3 years)

All patients will cease therapy with cerliponase alfa, if any of the following apply:

- The patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 14-month period excluding medical reasons for missed dosages); OR
- The patient is unable to tolerate infusions due to infusion related severe adverse events or any other clinical concerns that cannot be resolved and have been discussed with NHS England or the Managed Access Oversight Committee; OR
- The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit e.g.; cancer or multiple sclerosis; OR
- **The patient meets the stopping criteria as defined in sections 5.10 and 5.11.**

MAA starting and stopping criteria (2/3)

Link to – Treatment discontinuation rule

5.10 Stopping criteria for new patients aged 3 years and over who start treatment under this MAA or have been receiving treatment for less than 18 months

Patients aged 3 years and over, who have been receiving treatment for less than 18 months will be stopped if both of the following non-response criteria are met:

- A loss of more than two points (i.e. 3 or more points) on the CLN2 Rating Scale ML Score from baseline within eighteen months of the first infusion and a total CLN2 rating scale score of less than 2:
  - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks).

AND

- During the first eighteen months of treatment, a reduction in proxy reported patient quality of life of:
  - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference); **AND**
  - 0.23 drop in utility as measured by the EQ5D-5L **AND**
  - decline in CLN2 quality of life assessment of ≥ 15 points.

In the case of temporary illness, patients should be retested twice within 12 weeks to ensure that the decline is not solely due to a temporary illness.

MAA starting and stopping criteria (3/3)

Link to – Treatment discontinuation rule

5.11 Stopping criteria for existing patients aged 3 years and over who are currently on treatment, who have been receiving treatment for over 18 months

Patients who are 'currently on treatment' are defined as: (i) clinical trial patients; (ii) extended access programme; (iii) patients who started on treatment during the term of the MAA and have been receiving treatment for over 18 months. These patients should be stopped from receiving further treatment due to non-response, if they meet the following criteria:

- A loss of more than one point (i.e. 2 or more points) on the CLN2 Rating Scale ML Score, in the previous twelve months and a total CLN2 rating scale score of less than 2;
    - A loss is defined as a decline in CLN2 rating scale ML score that has persisted for 3 or more infusions (i.e. after 6 weeks)

OR

- Progression to an unreversed score of 0 on the CLN2 Rating Scales ML Score
    - Patients with a score of 0, should be retested twice within 12 weeks to ensure that the decline is not solely due to a temporary illness.

AND

- A reduction in proxy reported patient quality of life in the previous twelve-month treatment window of
    - ≥ 15 points on the PedsQL total score (which is three times the minimal clinically important difference);

AND

- 0.25 drop in utility as measured by the EQ5D-5L AND
- Decline in CLN2 quality of life assessment of ≥ 15point

Key issue: ECG monitoring costs

Company

- Base case does not include ECG monitoring costs during infusion of cerliponase alfa

EAG comments

- EAG's base case is in line with committees' preferred approach in HST12, includes ECG monitoring costs every 6 months for everyone receiving cerliponase alfa and at every infusion for those with previously detected clinically significant ECG-12 abnormalities
- Exclusion of ECG monitoring costs during infusion of cerliponase alfa is not in line with the SmPC
- Proportion requiring an ECG with each infusion was informed by the MAA cohort
  - ↳ 3% had clinically significant ECG-12 abnormalities at baseline rising to 27% at 3.5 years
  - ↳ Figures are an approximation → Using information in the CS you cannot identify the proportion of people receiving cerliponase alfa who have had at least one prior ECG clinically significant result and not everyone had a 3.5 years of follow up.
- This scenario is likely to underestimate the proportion that require ECG monitoring at every infusion.
- Proportion requiring an ECG with each infusion assumed in HST12 (Informed by Study 190-201/202)
  - ↳ 10% at baseline rising to 71% at 2 years

Should ECG monitoring costs be included in the model?

Abbreviations: CS, Company's submission; EAG, External assessment group; ECG, Electrocardiogram; HST, Highly specialised technology; MAA, Managed access agreement;

Uncertainty about trends in motor function and language

EAG comments

- Disease progression after long-term use of cerliponase alfa is currently unclear
  - ↳ Follow up in Study 190-202 and Study 190-203 has not extended beyond five years
- Rates of progression may vary across patients and within patients, with possible long periods of stability, or periods of rapid decline
- Rates of progression in more severe health states (ML state 1 or 2) is uncertain

Uncertainty about if benefits vary with age or disease progression at treatment initiation

EAG comments

- There is some suggestion in the trial that those who start treatment younger and with limited or no disease progression might have longer before disease progression, or slower disease progression
  - ↳ Number of people with an ML score of 6 at treatment initiation is small, and most have limited follow-up, so their disease progression is uncertain

Abbreviations: ML, Motor and Language;

Uncertainty around benefits on seizure prevention

EAG comments

- Data from the CLN2 MLVS scale showed that very few people on cerliponase alfa experienced a two-point loss on the seizure subscale → suggests that cerliponase alfa may be helping to prevent seizures or reduce their severity.
  - ↳ CLN2 MLVS scale provides limited information on the impact of seizures, and more detailed data on seizures was not available for most patients → Impact of any seizure prevention on QoL is uncertain

Uncertainty around non-neurological effects, including myoclonus and dystonia

EAG comments

- Available evidence on non-neurological outcomes (such as myoclonus, dystonia, and cardiac events) and on QoL is very limited
  - ↳ If cerliponase alfa extends life non-neurological outcomes may have a greater impact on HRQoL

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; HRQoL, Health related quality of life; MLVS, Motor, Language Vision, and Seizure; QoL, Quality of life;

Key issue: Neuro-disability mortality

Company

- Base case does not include neuro-disability mortality
- In the key trials no deaths were observed where neuro-disability was the cause

EAG comments

- EAG's base case is in line with committees' preferred approach in HST12, includes neuro-disability morality in all HSs
- The company's evidence is not sufficient due to its short-term nature
- **Scenario analysis** → Neuro-disability mortality included for HSs 6-9 based on clinical opinion

Key issue: Psychiatric/behavioural support costs

Company

- Base case does not include psychiatric/behavioural support costs based on clinical opinion

EAG comments

- EAG's base case is in line with committees' preferred approach in HST12, assumes that in both treatment groups patients >13 years in HSs 1-5 require psychiatric/behavioural support
- Clinical advice → the cost of psychiatric/behavioural support should be included in the model given the impact CLN2 disease has on behavioural symptoms

- Should neuro-disability mortality be included in the model?
- Should psychiatric/behavioural support costs be included in the model?

Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; EAG, External assessment group; HS, Health state; HST, Highly specialised technology;

Link between disease progression on motor and language domains, and other progressive symptoms

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Proportion of patients with progressive symptoms (other than seizures) is the same in both treatment group as elicited from company's clinical experts for CA	SoC	[redacted]	-0.28				
	CA	[redacted]	17.07	[redacted]	17.35	[redacted]	£300,000
Proportion of patients with progressive symptoms (other than seizures) is the same in both treatment group as from company's clinical experts for SoC	SoC	[redacted]	-0.28				
	CA	[redacted]	17.07	[redacted]	17.35	[redacted]	£300,000

Link to - Key issue scenario analyses – Applied to company base case (1/2)

Abbreviations: CA, Cerliponase alfa; SoC, Standard of care; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Baseline distribution across health states - Scenarios

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Clinical expert estimate of current clinical practice	SoC	[redacted]	-1.10	-	-	-	-
	CA	[redacted]	7.77	[redacted]	8.86	[redacted]	£153,704
Clinical expert estimate of clinical practice in 5-years time	SoC	[redacted]	-0.67	-	-	-	-
	CA	[redacted]	12.56	[redacted]	13.23	[redacted]	£256,021
As per original HST12	SoC	[redacted]	-0.59	-	-	-	-
	CA	[redacted]	13.25	[redacted]	13.84	[redacted]	£266,658
Study 190-203 starting distribution	SoC			-	-	-	
	CA			[redacted]	11.78	[redacted]	
MAA (new patients) starting distribution:	SoC			-	-	-	
	CA			[redacted]	7.82	[redacted]	

Link to - Key issue scenario analyses – Applied to company base case (1/2)

Abbreviations: CA, Cerliponase alfa; SoC, Standard of care; HST, Highly specialised technology; MAA, Managed access agreement; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Uncertainty around the initial stabilisation- Scenarios

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
80% of patients in HS1 at model entrance are initial stabilisers	SoC	[redacted]	-0.28				
	CA	[redacted]	16.02	[redacted]	16.30	[redacted]	£300,000
Reduction in transition probabilities (ML 6 stabilisers): 0%	SoC	[redacted]	-0.28				
	CA	[redacted]	14.05	[redacted]	14.34	[redacted]	£244,498
Reduction in transition probabilities (ML 6 stabilisers): 25%	SoC	[redacted]	-0.28				
	CA	[redacted]	15.37	[redacted]	15.66	[redacted]	£289,840
Duration of ML 6 stabilisation: 12 years	SoC						
	CA			[redacted]	18.52	[redacted]	
Reduction in transition probabilities (ML 6 stabilisers): 75%	SoC						
	CA			[redacted]	19.54	[redacted]	
Reduction in transition probabilities (ML 6 stabilisers): 100%	SoC						
	CA			[redacted]	22.11	[redacted]	

Link to - Key issue scenario analyses – Applied to company base case (1/2)

Evidence informing transition probabilities - Scenarios

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Source of transitions: All patients	SoC						
	CA			[redacted]	14.27	[redacted]	
Source of transitions: All patients (piecewise at 6 months)	SoC						
	CA			[redacted]	22.86	[redacted]	

Link to - Key issue scenario analyses – Applied to company base case (1/2)

Abbreviations: CA, Cerliponase alfa; SoC, Standard of care; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Transition probability estimates - Scenarios

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Backwards transitions to healthier states not allowed	SoC	[redacted]	-0.28				
	CA	[redacted]	12.09	[redacted]	12.38	[redacted]	£190,337

Link to - Key issue scenario analyses – Applied to company base case (2/2)

Abbreviations: CA, Cerliponase alfa; SoC, Standard of care; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Vision loss progression- Scenarios

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Linear decline with age between 6 and 10 years old	SoC	[redacted]	-0.28				
	CA	[redacted]	16.57	[redacted]	16.85	[redacted]	£300,000
As per original HST12 (driven by cumulative proportion of vision loss in the SoC)	SoC	[redacted]	-0.26				
	CA	[redacted]	16.20	[redacted]	16.45	[redacted]	£300,000

Link to - Key issue scenario analyses – Applied to company base case (2/2)

Abbreviations: HST, Highly specialised technology; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Treatment discontinuation rule - Scenarios

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Treatment discontinuation at HS7	SoC						
	CA			[redacted]	17.79	[redacted]	
No treatment discontinuation	SoC						
	CA			[redacted]	17.86	[redacted]	

Link to - Key issue scenario analyses – Applied to company base case (2/2)

Abbreviations: CA, Cerliponase alfa; SoC, Standard of care; HS, Health state; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Treatment specific health state utilities – Scenarios (1/2)

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Utilities informed by MAA for cerliponase alfa; SoC health state utilities calculated by assuming the same change in utilities between health states for those treated with SoC in Gissen et al., 2021	SoC	[redacted]	-0.89				
	CA	[redacted]	15.32	[redacted]	16.20	[redacted]	£300,000
Utilities informed by MAA for cerliponase alfa; SoC health state utilities calculated by assuming the same difference in utilities between treatments at each health state as in Gissen et al., 2021.	SoC	[redacted]	0.11				
	CA	[redacted]	15.62	[redacted]	15.51	[redacted]	£300,000

Link to - Key issue scenario analyses – Applied to company base case (2/2)

Abbreviations: CA, Cerliponase alfa; MAA, Managed access agreement; SoC, Standard of care; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Treatment specific health state utilities – Scenarios (2/2)

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Source of utility values: MAA	SoC						
	CA			[redacted]	16.20	[redacted]	
Gissen 2021, treatment-independent utility values	SoC						
	CA			[redacted]	16.88	[redacted]	
MAA (all patients), treatment-independent utility values	SoC						
	CA			[redacted]	15.03	[redacted]	

Link to - Key issue scenario analyses – Applied to company base case (2/2)

Abbreviations: CA, Cerliponase alfa; MAA, Managed access agreement; SoC, Standard of care; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

ECG monitoring costs - Scenarios

Table: Scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Including ECG monitoring costs	SoC	[redacted]	-0.28				
	CA	[redacted]	17.07	[redacted]	17.35	[redacted]	£300,000

Link to - Key issue scenario analyses – Applied to company base case (2/2)

Abbreviations: CA, Cerliponase alfa; ECG, Electrocardiogram; SoC, Standard of care; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;

Company deterministic scenario analysis

Table: Company scenario analyses (deterministic)

Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base-case ICER
Company base case	[redacted]	**17.35**	[redacted]	[redacted]
Scenario: AE rates doubled	[redacted]	17.33	[redacted]	[redacted]
Scenario: AE rates set to zero	[redacted]	17.37	[redacted]	[redacted]
Scenario: including ICV-related infection cost and disutility	[redacted]	17.35	[redacted]	[redacted]
Scenario: including neuro-disability mortality risk	[redacted]	17.31	[redacted]	[redacted]
Scenario: including infection-related mortality in ML score 0	[redacted]	17.35	[redacted]	[redacted]
Scenario: Caregiver disutility not applied for patients in residential care	[redacted]	17.37	[redacted]	[redacted]
Scenario: Sibling disutility not applied to patients in residential care	[redacted]	17.37	[redacted]	[redacted]
Scenario: Neither caregiver nor sibling disutility applied to patients in residential care	[redacted]	17.38	[redacted]	[redacted]
Scenario: Include testing costs	[redacted]	17.35	[redacted]	[redacted]

Abbreviations: AE, Adverse events; ICER, Incremental cost-effectiveness ratio; ICV, Intracerebroventricular; QALY, Quality-adjusted life year;

EAG additional scenarios

Table: EAG additional scenario analyses – Applied to company base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
Neuro-disability mortality included for HS6-9	SoC	[redacted]	-0.28				
	CA	[redacted]	17.07	[redacted]	17.36	[redacted]	£300,000
Carer and sibling disutilities for cerliponase alfa are the same as for the SoC values	SoC	[redacted]	-0.28				
	CA	[redacted]	16.87	[redacted]	17.15	[redacted]	£300,000
Carer and sibling disutilities for cerliponase alfa correspond to 75% of the SoC values	SoC	[redacted]	-0.28				
	CA	[redacted]	16.97	[redacted]	17.25	[redacted]	£300,000
Including psychiatric/behavioural support costs	SoC	[redacted]	-0.28				
	CA	[redacted]	17.07	[redacted]	17.35	[redacted]	£300,000

Abbreviations: CA, Cerliponase alfa; HS, Health state; SoC, Standard of care; CoE, Cost effectiveness; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; QALY, Quality-adjusted life year;