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

For Zoom – contains redacted information

Highly Specialized Technology Appraisal Committee [5 September 2024]

Chair: Paul Arundel

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Company: BioMarin Pharmaceuticals

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

- ✓ **Recap of ACM1**
- ❑ Key Issues
- ❑ 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

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 Study 190-203
  - 3 long term safety studies and 2 supplementary studies

ACM1

- The committee did not publish draft guidance it instead asked the company to provide additional analysis it needed to make decisions on issues that were key for decision making including:
  - Scenarios with starting and stopping rules & removal of background costs

Abbreviations: ACM, Appraisal committee meeting; CLN2, Neuronal ceroid lipofuscinosis type 2; HST, Highly specialised technology; MA, Managed access; 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 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 proposed a confidential commercial arrangement which has not (yet) been approved by NHS England, and so not incorporated by NICE

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

Clinical trial results

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

RECAP

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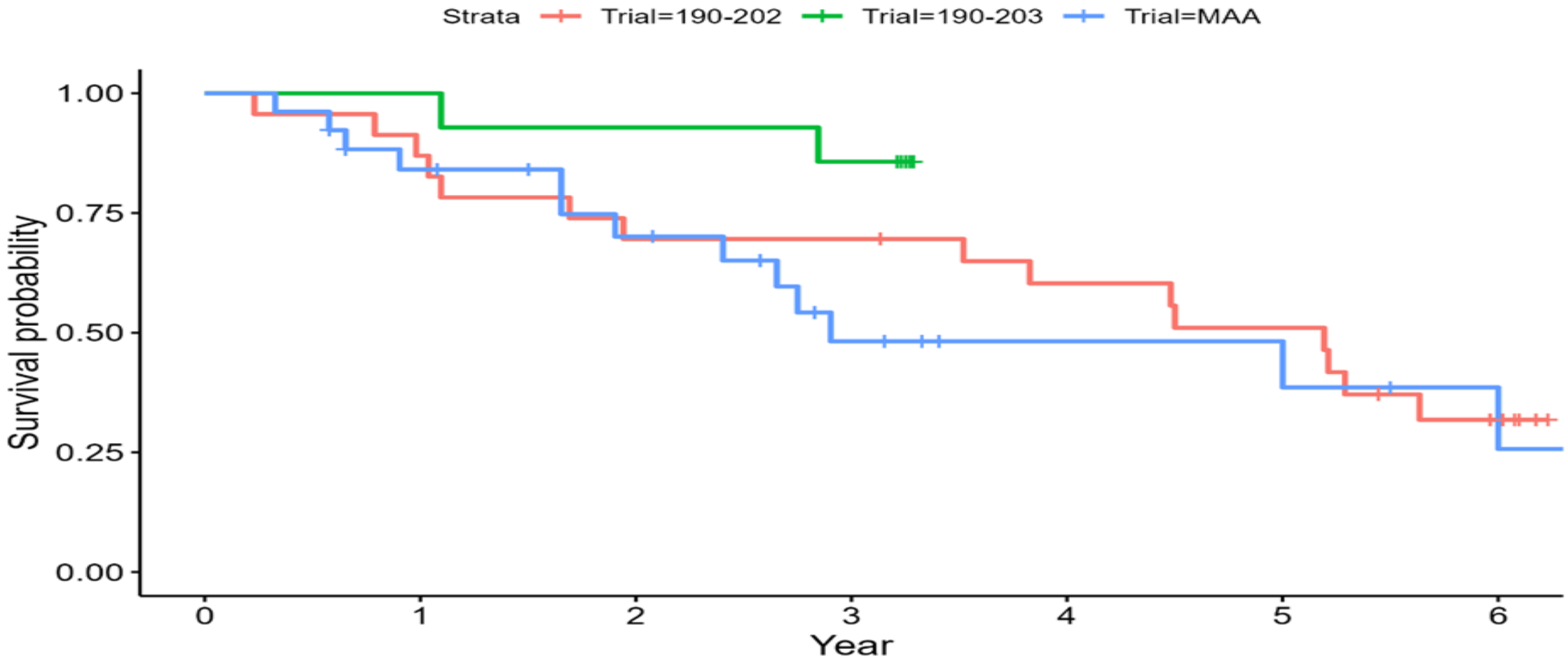
Abbreviations: CLN2, Neuronal ceroid lipofuscinosis type 2; FAS, Full analysis set; HR, Hazard ratio; ML, Motor and Language; NH, Natural history;

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;

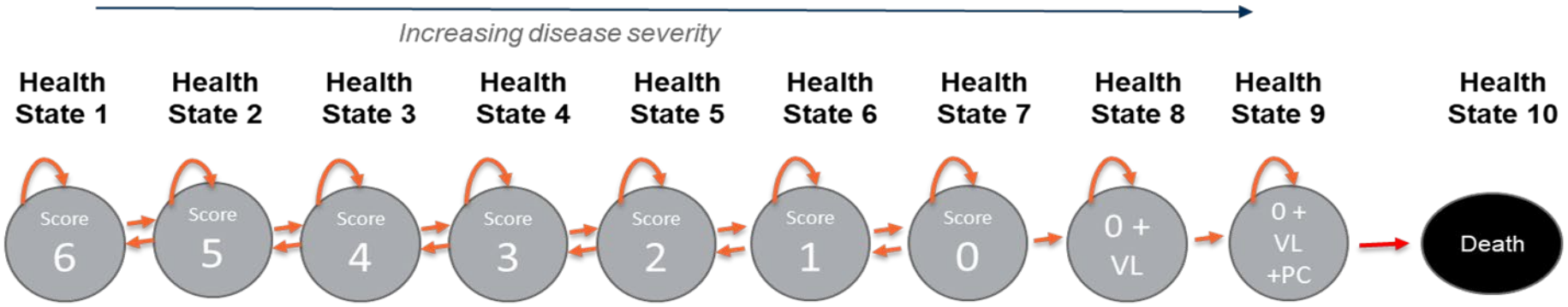
Unresolvable clinical uncertainty

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

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 from ACM1

The committee reached conclusions on several issues

Issue	Committee preferred assumption (ACM1)
Structural link between disease progression and other progressive symptoms	A link between progression in terms of motor and language symptoms to 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 proportion of people that experience progressive symptoms in each arm was suitable for decision making
Initial stabilisation	80% of people that start cerliponase alfa in HS1 would be 'initial stabilisers'
Robustness of transition probability estimates in HS1-7	The company's method to estimate transition probabilities should be used Backward transitions to healthier HSs should be allowed
Vision loss progression	Cerliponase alfa has no impact on vision loss
Health state utilities	HS utilities from Gissen et al. (2021) should be used
Other issues	ECG monitoring* & psychiatric and behavioural costs should be included Neuro-disability mortality should be included in all health states.

* The company has submitted analysis exploring alternative approaches to including ECG monitoring costs

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

Additional analysis requested after ACM1

The committee requested further information to aid its decision making

Issue	Committees view
Baseline distribution across health states	Believed there was not sufficient evidence for deciding what the baseline distributions is ↳ EAG's and company's assumptions were too optimistic
Evidence informing transition probabilities	Preferred evidence source is the 'all patients' pooled dataset ↳ Using Study 190-203 was unrealistic without newborn screening ↳ Requested a scenario using the pooled dataset but excluding the MAA cohort
Treatment starting rule	Requested additional analysis that considers the inclusion of starting and stopping rules
Treatment discontinuation rule	
Non-reference-case-analysis with background care costs removed	Requested additional analysis with background care costs removed *(In line with section 4.4.16 of NICE's manual (2022))* ↳ Rationale for removing specific costs and any assumptions used should be clearly documented

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; MAA, Managed access agreement;

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

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

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

Committee ACM1

- Company's and EAG's base case assumptions were too optimistic
  - ↳ Clinical experts explained that many patients continue to be diagnosed with ML scores < 5 and people will continue to be diagnosed with ML scores < 5 unless newborn genetic screen is widely rolled out
  - ↳ No evidence was provided that newborn screening is currently available or will be in the near future
- Requested additional analysis using data taken from current clinical practice that excludes patients where diagnosis or treatment initiation was delayed because of COVID-19
  - ↳ The baseline distribution provided by one of the clinical experts at ACM1 was plausible and could be considered in a scenario analysis

Company response

- Updated base case uses the EAG's clinical experts estimate of "Clinical practice in 5-year time"
  - ↳ This was the best estimate of a baseline distribution unaffected by COVID-19
  - ↳ Analysis using data taken from clinical practice was not possible because COVID-19 may still be affecting diagnosis and all the data from the MAA database and clinical trials were affected by either cerliponase alfa not being available when people were diagnosed or COVID-19

EAG comment

- EAG's updated base case uses the baseline distribution provided by one of the clinical experts at ACM1
  - ↳ Choice of baseline distribution made in the absence of a committee preferred assumption

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

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

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

Health State	ML Score	Study 190-203, <3 years (N=8)	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 submission (Patients treated at GOSH) (N=19)**	*ACM1 CE*
Age		2	-	-	4	4.5	*3.5*	*26.3%**<4 73.6% 4 - 4 years 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

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

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

Key issue: Treatment starting rule

Committee ACM1

- Requested analysis exploring starting rules to identify a subgroup of individuals for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost effective

Company response

- Do not endorse or support the inclusion of starting criteria → Starting ML scores can be improved without introducing starting criteria → Is committed to the development of an early diagnosis programme
- Patient groups and parents would strongly oppose the inclusion of starting criteria
- Clinical trial evidence does not support the implementation of starting criteria
- Provided "highly exploratory" scenario analysis
  - ↳ ML score 5 and 6 (Baseline distribution reweighted) / ML score 6 only / ML score 6 and a starting age of 0 (reflecting newborn screening)

EAG comment

- Scenario analysis shows that starting treatment at higher ML scores results in more QALY gains but increased costs of treatment (mainly cerliponase alfa related costs)
  - ↳ Starting treatment at higher ML scores is associated with lower ICERs
- Overall evidence available is not appropriate to guide the establishment of starting criteria

- Is there a starting rule that suggests cerliponase alfa is particularly clinically and cost effective for a subgroup of individuals?

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Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; ML, Motor and Language; QALY, Quality-adjusted life year;

Key issue: Treatment discontinuation rule (1/2)

Committee ACM1

- Clinical experts: Treatment likely continues to provide benefits even with significantly progressed disease
  - ↳ Would expect treatment discontinuation when people reach HS 6/7 and after considering the advantages and disadvantages alongside the family's perception of QoL
- Patient experts: Caregivers would be best positioned and willing to make decisions about discontinuation
- Requested analysis exploring treatment discontinuation rules to identify a subgroup of individuals for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost effective

Company response (base case assumes people discontinue treatment at an ML score of 1)

- Do not endorse or support the inclusion of treatment discontinuation rules
- Patient groups and parents would strongly oppose the inclusion of a treatment discontinuation rule
- Evidence from the clinical trials does not support the implementation of a treatment discontinuation rule
- Nobody has discontinued treatment because they reached the stopping criteria in the MAA
- Clinical experts:
  - ↳ Currently the decision to discontinue would be on a case-by-case basis and depend on factors such as ML score, PROs and the intensity of progressive symptoms *(could not be incorporated into the model)*
  - ↳ ML score alone is not appropriate for deciding if treatment should be discontinued
- Treatment discontinuation is not a key driver of cost effectiveness
  - ↳ In all scenarios the percentage change in the ICER was proportional to change in the CoE threshold

Abbreviations: ACM, Appraisal committee meeting; CoE, Cost effectiveness; HS, Health state; ICER, Incremental cost-effectiveness ratio; MAA, Managed access agreement; ML, Motor and Language; PRO, Patient-reported outcomes; QoL, Quality of life;

Key issue: Treatment discontinuation rule (2/2)

EAG comments (base case assumes people discontinue treatment at an ML score of 0)

- Provided scenario analysis applied to its base case that explored the impact of different stopping rules for people staring treatment at different ML scores (ML 4, ML5 and ML 6)
  - ↳ Regardless of the ML score when treatment is started discontinuing treatment at lower ML scores is associated with higher ICERs
  - ↳ When treatment is started with an ML score of 4 or 5 the ML score when treatment is discontinued has no impact on the implied cost-effectiveness threshold
  - ↳ When treatment is started with an ML score of 6 discontinuing treatment at lower ML scores is associated with higher implied cost-effectiveness thresholds because of increased QALY gains for cerliponase alfa vs. SoC when only patient utilities are considered
- The scenario analyses is highly exploratory and not equivalent to subgroup analyses → It does not allow the identification of subgroups for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost-effective
  - ↳ The underlying clinical effectiveness evidence is not specific to the subpopulations defined by the starting and stopping criteria in each analysis
- Overall evidence available is not appropriate to guide the establishment of stopping criteria

- In what health state would people discontinue cerliponase alfa?
- Is there a discontinuation rule that suggests celiponase alfa is particularly clinically and cost effective for a subgroup of individuals?

Abbreviations: EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; ML, Motor and Language; QALY, Quality-adjusted life year; SoC, Standard of care;

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

Committee ACM1

- Preferred data source was the pooled data from Study 190-201/202, Study 190-203 and the MAA
- Data from Study 190-203 likely reflects a population that starts treatment younger and with less progressed disease than is currently seen in the NHS
- The 'all patients' pooled dataset may introduce bias against cerliponase alfa due to the COVID-19 pandemic and past delays between diagnosis and receiving treatment
  - ↳ Excluding the MAA cohort may mitigate some of the bias caused by the COVID-19 pandemic
- Requested additional analysis using the pooled dataset but excluding the MAA cohort

Company response (updated base case: Study 190-203)

- Provided requested analysis using pooled dataset but excluding the MAA cohort
- Data from Study 190-201/202 and the MAA includes transitions from progressed patients who did not have access to cerliponase alfa at the time of diagnosis
- Data from Study 190-201 includes patients who enrolled in the dose-escalation phase some of which experienced disease progression

Abbreviations: ACM, Appraisal committee meeting; EAP, Expanded access program; MAA, Managed access agreement;

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

EAG comments (updated base case: pooled data from study 190-201/202, Study 190-203 and the MAA)

- The pooled 'all patients' data is the most appropriate source of evidence
  - ↳ Reflects most of the existing evidence due to the sample size and overall length of follow-up
- Using Study 190-203 introduces considerable uncertainty and potential bias favouring cerliponase alfa
  - ↳ Due to the small numbers of patients and the limited duration of follow-up (Only some patients were followed up to 6 years)
  - ↳ The population in Study 190-203 may reflect a population younger and at an earlier point of disease progression than in clinical practice

* See appendix – Length of follow up by study

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

Abbreviations: EAG, External assessment group; MAA, Managed access agreement;

Key issue: ECG monitoring costs

Committee ACM1

- ECG monitoring costs should be included in line with the summary of product characteristics

Company response

- Updated base case:
  - ↳ ECG included at every infusion for a proportion of patients with a history of bradycardia, conduction disorder + one annual cardiologist appointment for all patients
- Clinical advice: “Cardiac-normal patients” would not receive ECGs in clinical practice

EAG comments

- Base case:
  - ↳ The same as the company's updated base case, but also includes the cost of an ECG every 6 months for all patients
- The assumption that the proportion of patients who have cardiac abnormalities remains constant beyond 3.5 years may underestimate the proportion of patients with cardiac abnormalities over time and therefore the costs associated with ECG monitoring
  - ↳ So, it isn't excessively conservative to maintain the assumption of ECG monitoring every 6 months for all patients (In line with the summary of product characteristics)

- Should the cost of an ECG every 6 months for all patients be included?

NICE

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; ECG, Electrocardiogram;

Key issue: Non-reference-case-analysis (1/2)

Background

- **NICE Manual (Section 4.4.16):** *"In cases where a technology increases survival in people for whom the NHS is currently providing care that is expensive or would not be considered cost effective at NICE's normal levels, the committee may consider alongside the reference-case analysis a non-reference-case analysis with the background care costs removed. The committee will consider in its decision making both the reference-case and non-reference-case analyses, taking into account the nature of the specific circumstances of the evaluation including the population, care pathway and technology, as well as:*
  - *The extent to which the cost effectiveness of the technology is driven by factors outside its direct costs and benefits*
  - *If the NHS is already providing care that would not be considered cost effective at NICE's normal levels*
  - *If the high-cost care is separate from direct, intrinsic consequences of the technology (such as a side effect or administration cost)*
  - *The extent to which commercial solutions would address the issue."*

Committee ACM1

- Requested analysis with background care costs removed in line with section 4.4.16 of the manual
  - ↳ The rationale for removing specific background care costs and any structural assumptions used in the analysis should be clearly documented

Abbreviations: ACM, Appraisal committee meeting

Key issue: Non-reference-case-analysis (2/2)

Company response

- Updated base case:
  - ↳ Removed health state, vision loss, psychiatric and behavioural support and residential care costs from both arms
  - ↳ The cerliponase alfa arm only included the costs associated with the drug acquisition, administration, monitoring and managing adverse treatment effects of cerliponase alfa
- Increased survival associated with cerliponase alfa results in increased background costs that are not direct, intrinsic consequences of the technology

EAG comments

- Updated base case: Includes background costs in both arms
  - ↳ The removal of background costs was only requested as a non-reference-case analysis

- Should the non-reference-case analyses be considered as part of decision making?

Abbreviations: EAG, External assessment group;

Equality

Company

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

Clinical expert

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

Innovation

Company

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

Information not captured in the evaluation

Company

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

Clinical expert

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

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

Company and EAG updated base case assumptions (1/2)

Table: Assumptions in company and EAG updated base case

Assumption	Company updated base case	EAG updated 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: 50%, HS2: 35%, HS3: 12.5%, HS4, 2.5%**	**HS1: 28.5%, HS2: 28.5%, HS3: 43%, HS4, 0%**
Initial stabilisation	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 updated base case assumptions (2/2)

Table: Assumptions in company and EAG updated base case

Assumption	Company updated base case	EAG updated base case
Vision loss	Cerliponase alfa has no impact on progression to vision loss	
Treatment discontinuation	**In health state 6 (ML score 1)**	**In health state 7 (ML score 0)**
Health state utilities	Gissen et al., 2021	
ECG monitoring costs	**Excluded the cost of an ECG every 6 months for all patients**	**Included the cost of an ECG every 6 months for all patients**
Neuro-disability mortality	Included	
Psychiatric/behavioural support costs	Included	
Background care 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.

- 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

NICE

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

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

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

NICE National Institute for Health and Care Excellence

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

Base case results

Company corrected* deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	CoE threshold (£/QALY)
SoC	[redacted]	[redacted]	-	-	-	
Cerliponase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£194,964

EAG deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	CoE threshold (£/QALY)
SoC	[redacted]	[redacted]	-	-	-	
Cerliponase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£100,000

*The EAG have corrected the company's model by extending the company's correction to the treatment effect after cerliponase alfa discontinuation

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

Baseline distribution across health states - scenarios

Table: Scenario analyses – applied to EAG base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
EAG base-case + Baseline characteristics as per clinical opinion of current practice in 5-year time (company's corrected base-case)	SoC	[redacted]	[redacted]				
	CA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£137,428
EAG base-case + Baseline characteristics as per EAG's original base-case (HS1 50%, HS2 50%)	SoC	[redacted]	[redacted]				
	CA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,405

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

Source of transition probabilities- scenarios

Table: Scenario analyses – applied to EAG base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
EAG base-case + Source of transition probabilities: Pooled data from Study 190-201/202 and Study 190-203 excluding MAA, matched to Study 190-901	SoC	[redacted]	[redacted]				
	CA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,460

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

Non-reference-case-analysis - scenarios

Table: Scenario analyses – applied to EAG base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
EAG base-case + Excluding background costs	SoC	[redacted]	[redacted]				
	CA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£100,000

Treatment discontinuation rule - scenarios

Table: Scenario analyses – applied to EAG base case

Scenario		Costs	QALYs	Inc cost	Inc QALYs	ICER	CoE Threshold
EAG base case + Stopping rule at ML 1 (HS 6)	SoC	[redacted]	[redacted]				
	CA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£100,000
EAG base case (Stopping rule at ML 0 (HS 7))	SoC	[redacted]	[redacted]				
	CA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£100,000
EAG base case + No discontinuation rule	SoC	[redacted]	[redacted]				
	CA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£126,618

Abbreviations: CoE, Cost effectiveness; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; ML, Motor and Language; QALY, Quality-adjusted life year;

Starting and discontinuation rules – scenarios (1/3)

Table: Scenario analyses – applied to EAG base case

Scenario		ICER (per QALY)	% change from base-case ICER	CoE threshold £/QALY	% change from base-case CoE threshold
EAG base-case		[redacted]	-	£100,000	-
Starting ML	Treatment stop ML				
6	No stopping	[redacted]	[redacted]	£239,004	139%
	0	[redacted]	[redacted]	£220,299	120%
	1	[redacted]	[redacted]	£192,462	92%
	2	[redacted]	[redacted]	£176,792	77%
	3	[redacted]	[redacted]	£165,133	65%
	4	[redacted]	[redacted]	£157,399	57%

Abbreviations: CoE, Cost effectiveness; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; ML, Motor and Language;

Starting and discontinuation rules – scenarios (2/3)

Table: Scenario analyses – applied to EAG base case

Scenario		ICER (per QALY)	% change from base-case ICER	CoE threshold £/QALY	% change from base-case CoE threshold
EAG base-case		[redacted]	-	£100,000	-
Starting ML	Treatment stop ML				
5	No stopping	[redacted]	[redacted]	£100,000	0%
	0	[redacted]	[redacted]	£100,000	0%
	1	[redacted]	[redacted]	£100,000	0%
	2	[redacted]	[redacted]	£100,000	0%
	3	[redacted]	[redacted]	£100,000	0%
	4	[redacted]	[redacted]	£100,000	0%

Abbreviations: CoE, Cost effectiveness; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; ML, Motor and Language;

Starting and discontinuation rules – scenarios (3/3)

Table: Scenario analyses – applied to EAG base case

Scenario		ICER (per QALY)	% change from base-case ICER	CoE threshold £/QALY	% change from base-case CoE threshold
EAG base-case		[redacted]	-	£100,000	-
Starting ML	Treatment stop ML				
4	No stopping	[redacted]	[redacted]	£100,000	0%
	0	[redacted]	[redacted]	£100,000	0%
	1	[redacted]	[redacted]	£100,000	0%
	2	[redacted]	[redacted]	£100,000	0%
	3	[redacted]	[redacted]	£100,000	0%

Abbreviations: CoE, Cost effectiveness; EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; ML, Motor and Language;

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

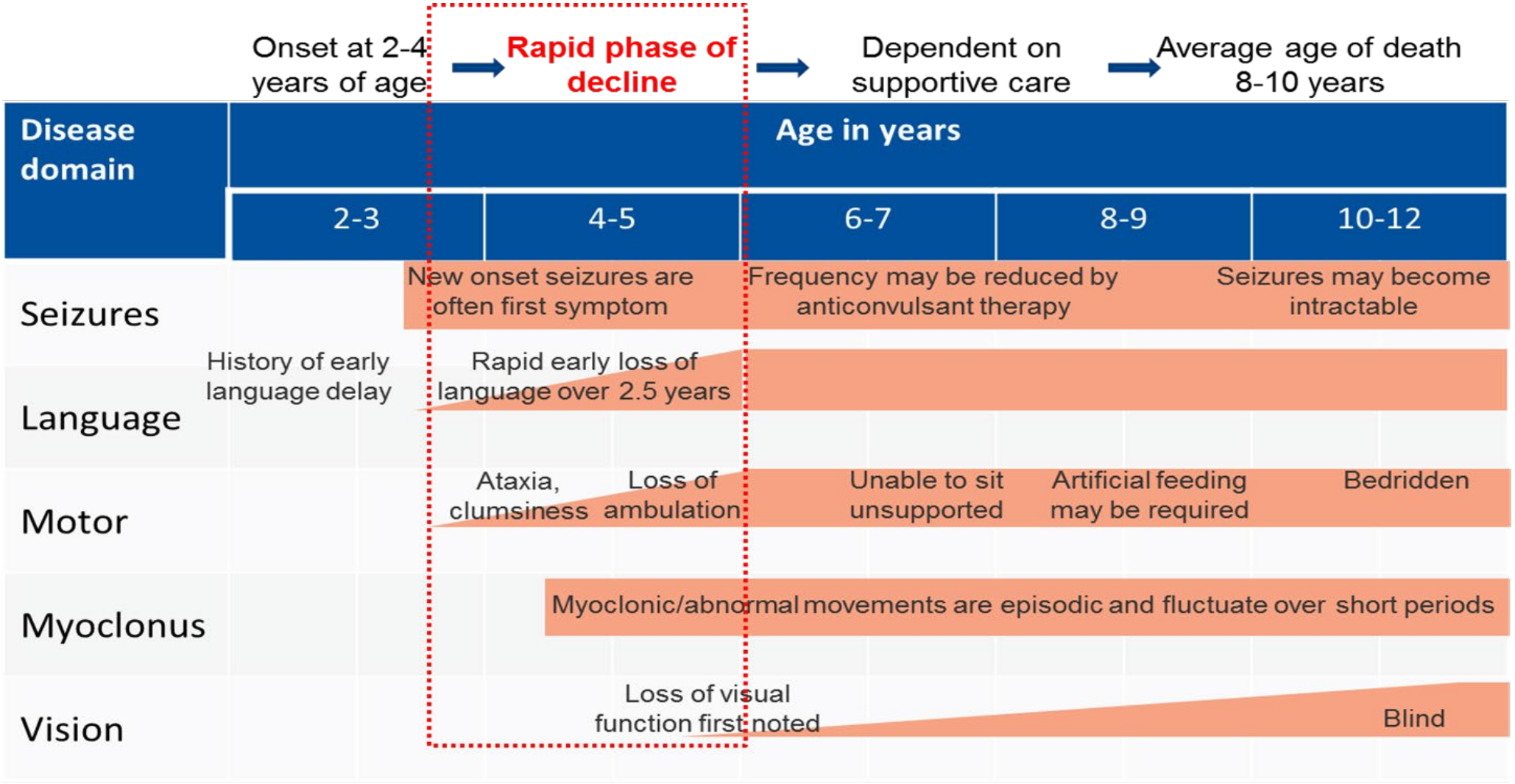
- Based on laboratory testing following clinical suspicion → Demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) and the identification of pathogenic variants in both alleles of the *TPP1/CLN2* gene

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)

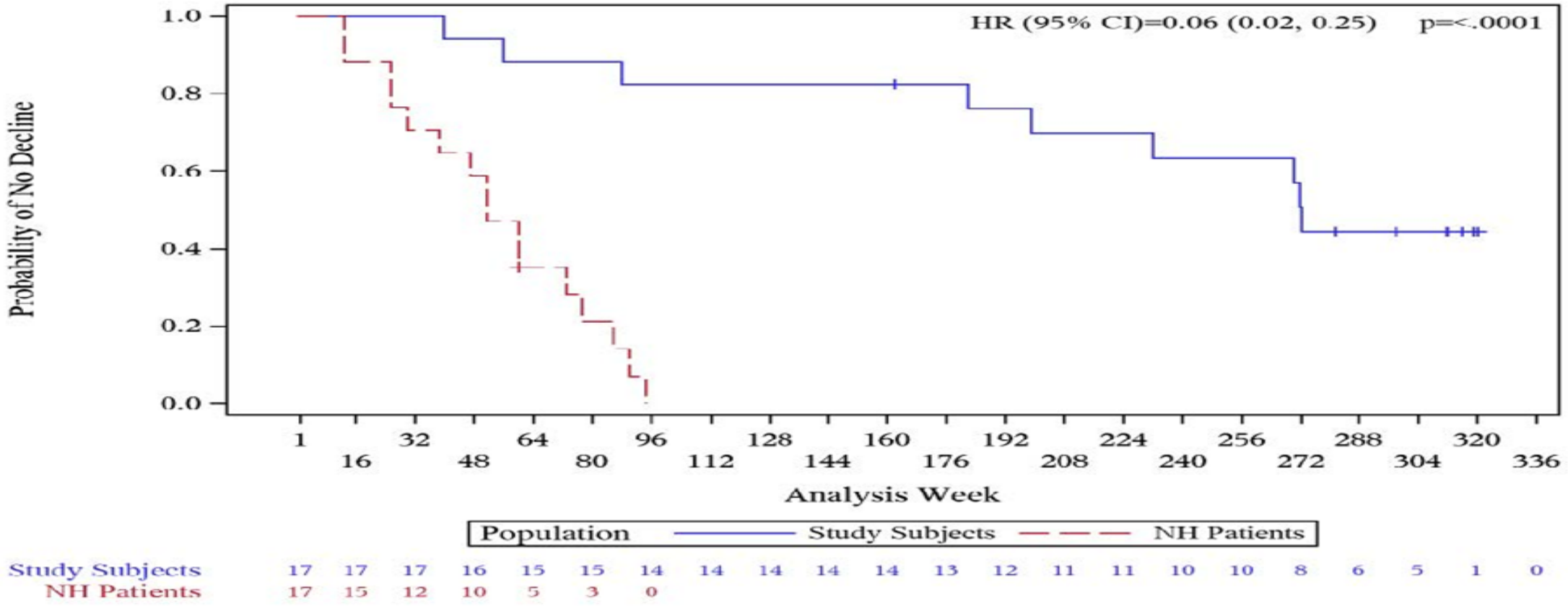
	NH and MAA FAS matched patients		NH and MAA new starter matched patients	
	NH (n=26)	MAA FAS (n=26)	NH (n=17)	MAA new starters (n=17)
Age at baseline (years)				
n	26	26	17	17
Mean (SD)	4.35 (1.11)	4.37 (1.07)	4.53 (1.18)	4.56 (1.10)
Median (Min, Max)	4.25 (1.75,8.75)	4.33 (1.72, 8.5)	4.25 (3.33, 8.75)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



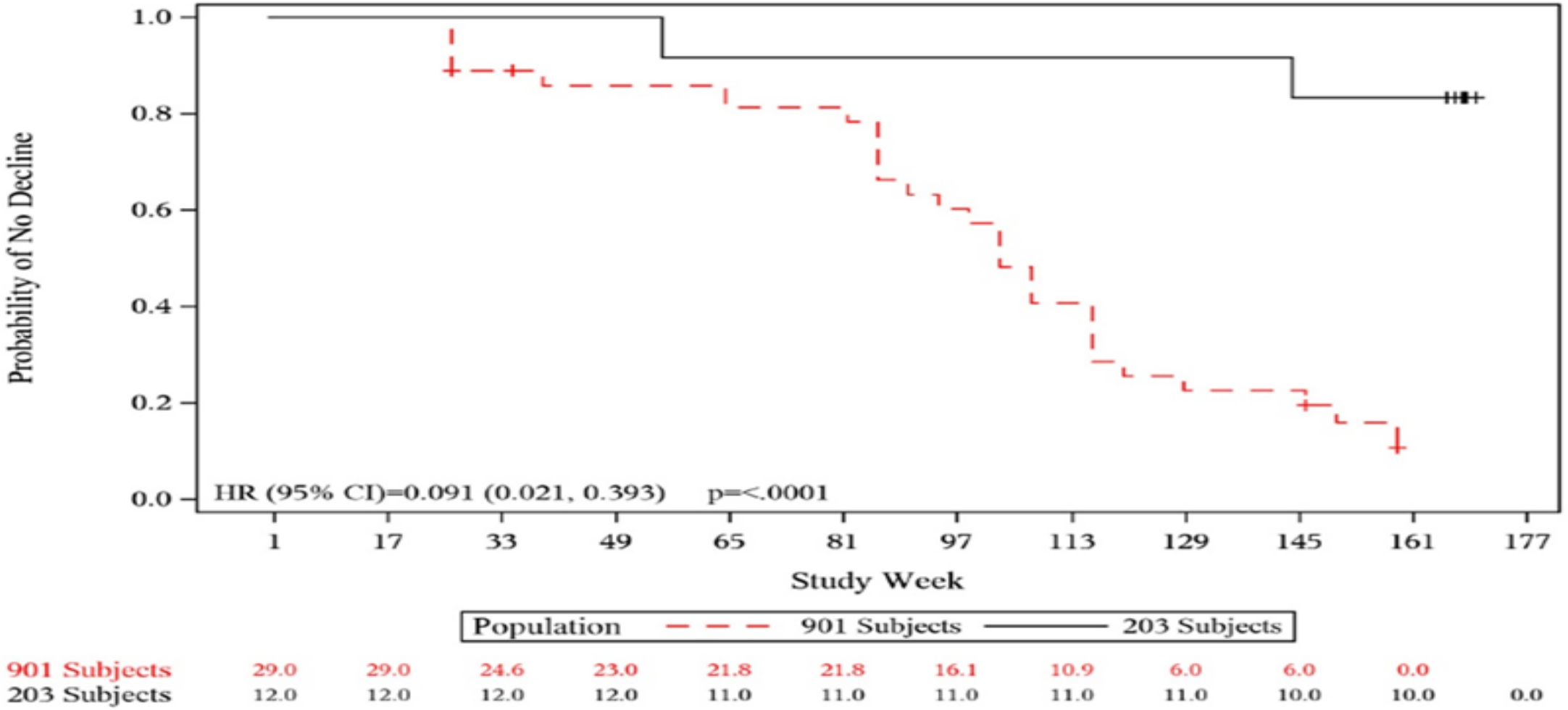
Link to – Clinical trials results

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)

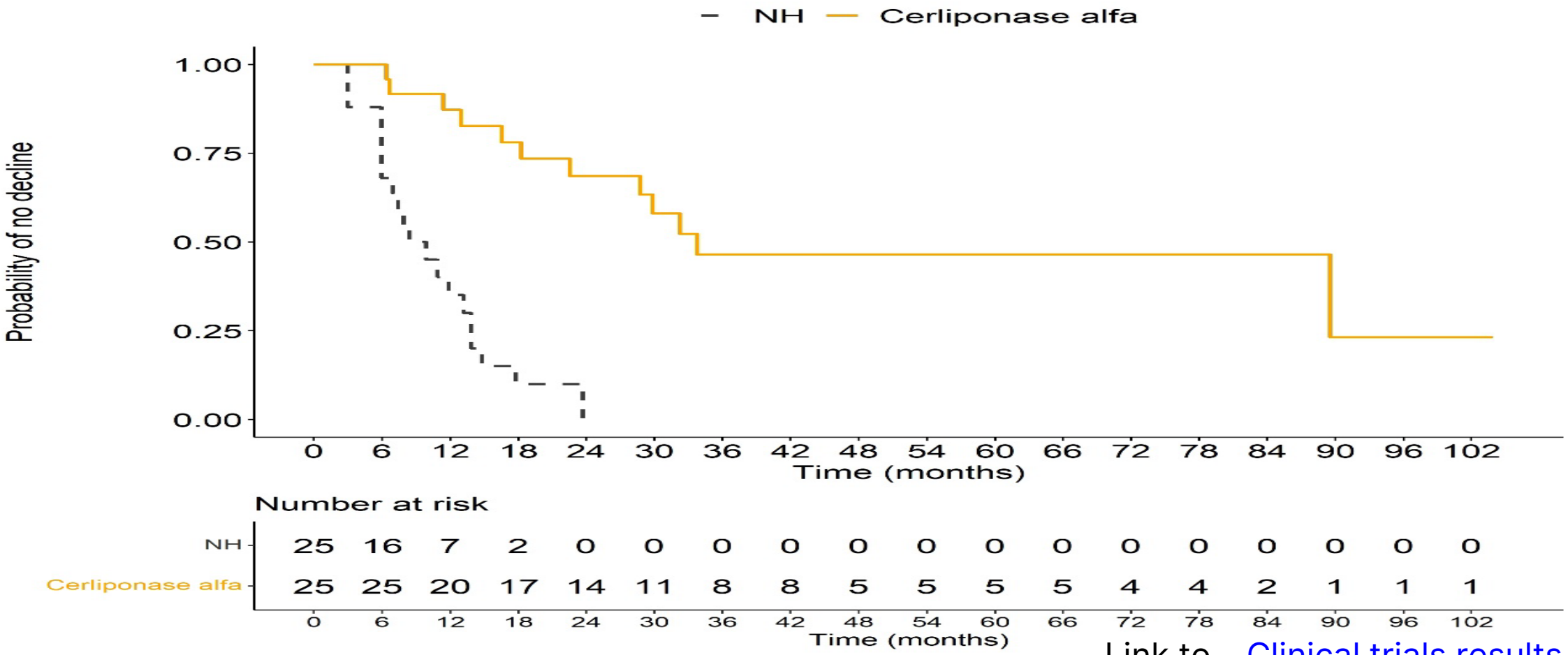


Abbreviations: ML, Motor and Language; NH, Natural history;

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)



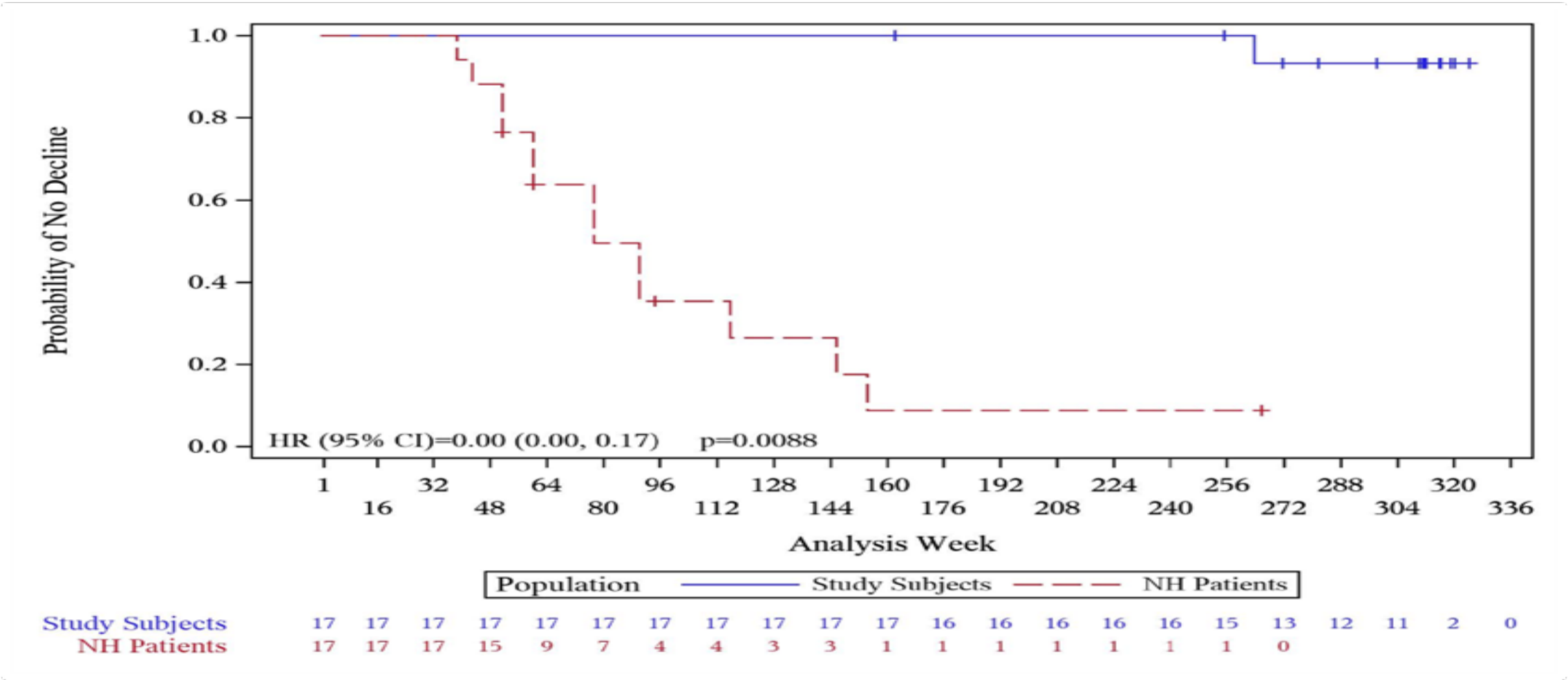
Link to – Clinical trials results

NICE

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)



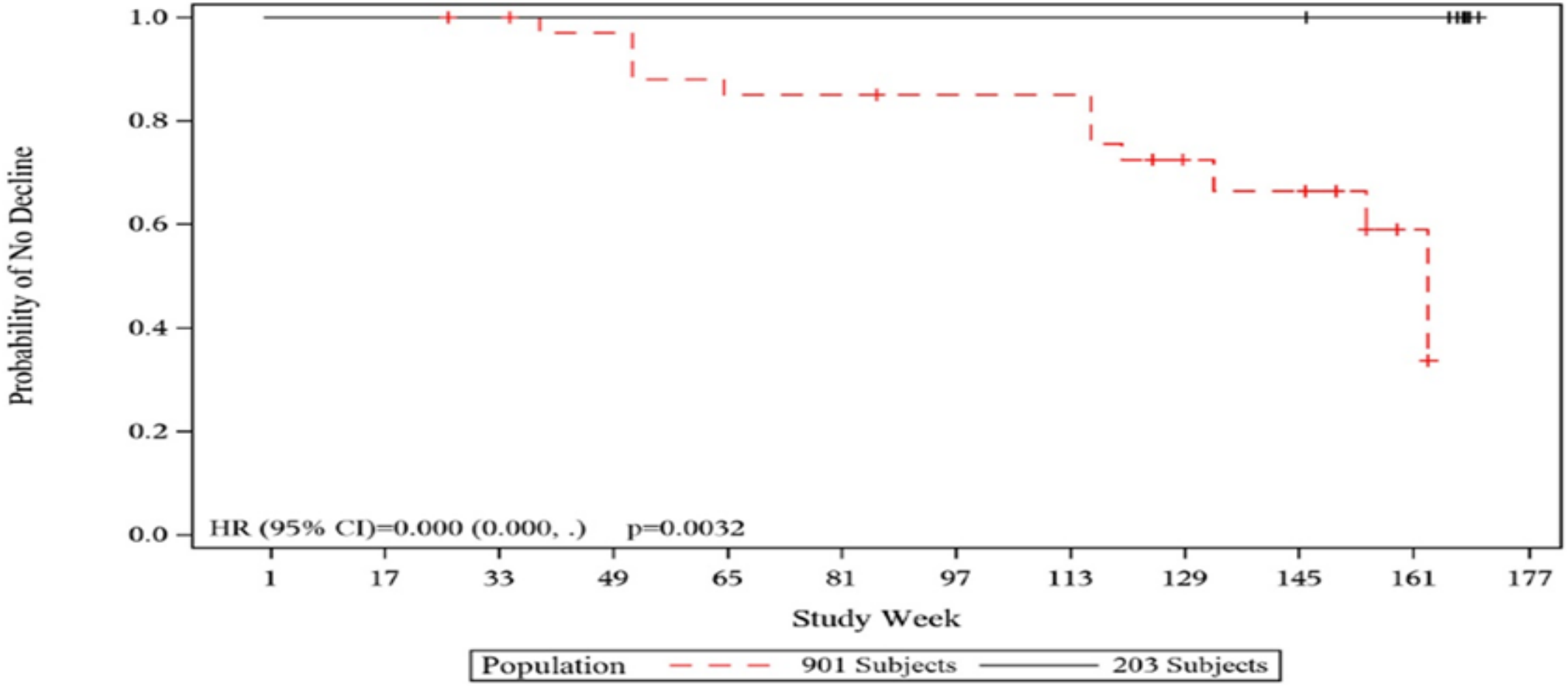
Link to – Clinical trials results

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)



901 Subjects	29.0	29.0	27.8	26.2	23.0	23.0	21.7	21.7	14.5	13.3	2.8	0.0
203 Subjects	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	11.0	0.0

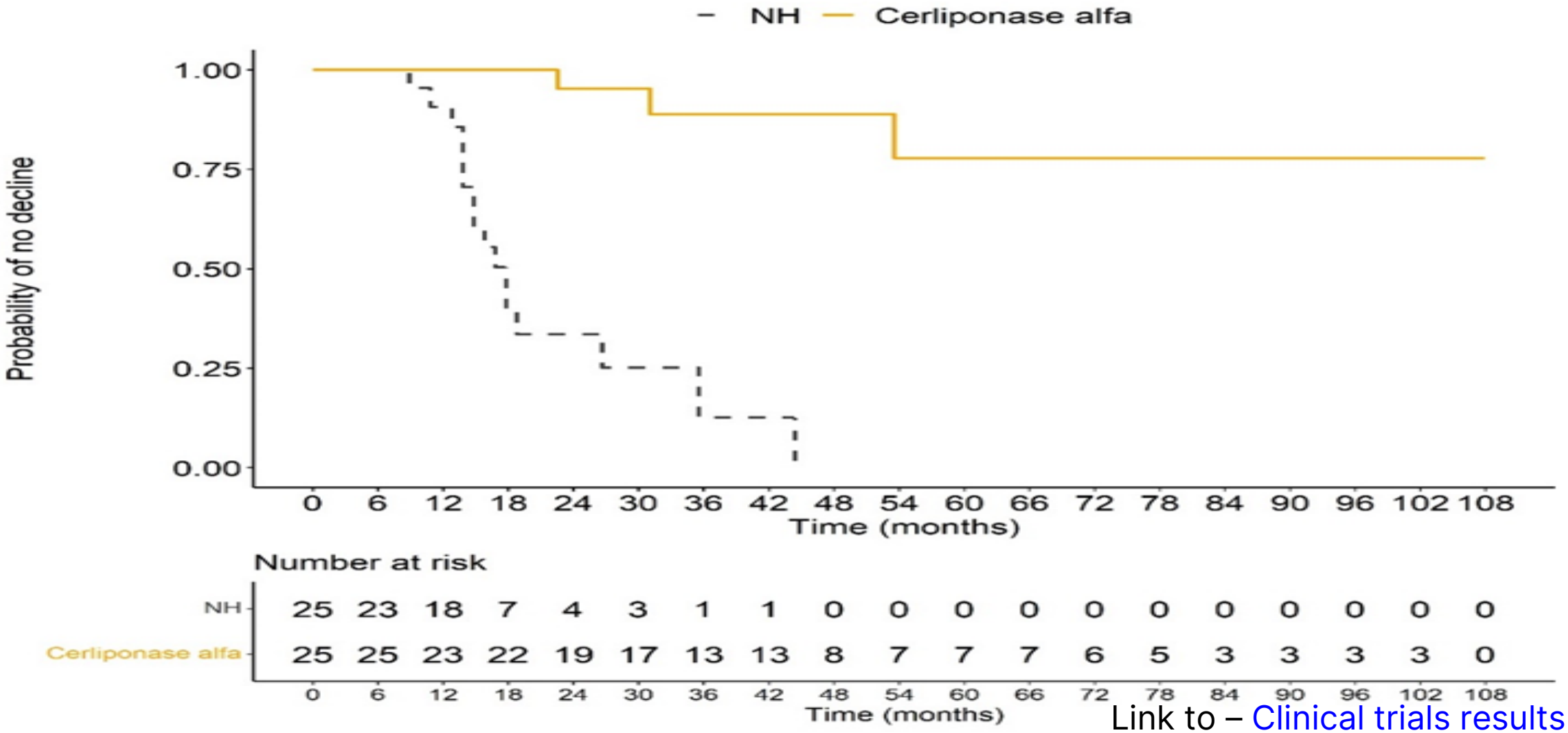
Link to – Clinical trials results

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)

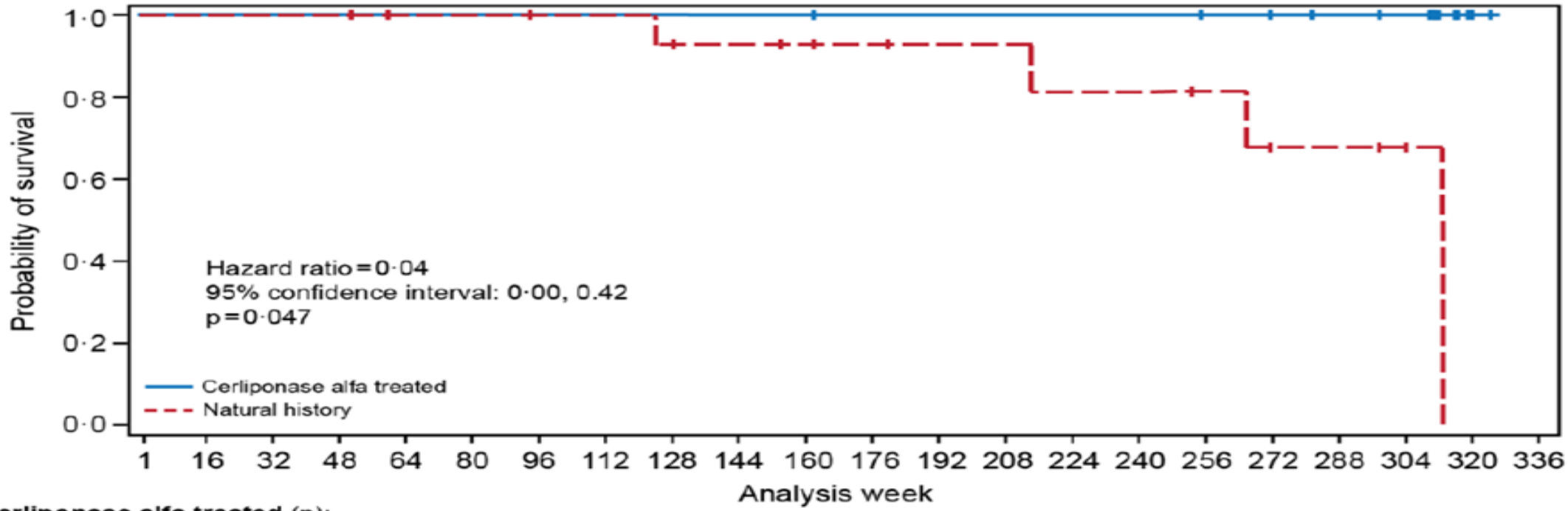


Link to – Clinical trials results

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		??
Rational if not used in the model	Additional information on the safety and tolerability of cerliponase alfa administration in patients with CLN2 disease was not used to inform the model		
Locations	US	US, Germany, Italy, UK	Denmark, France, the Netherlands, Sweden, Italy, Germany, Romania, UK
No of UK patients	0	6	7

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

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

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)

NICE

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 (3/3)

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)

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

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.

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

RECAP

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.**

RECAP

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.

RECAP

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

Length of follow up by study

Link to – Evidence informing transition probabilities (2/2)

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

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

Abbreviations: MAA, Managed access agreement; SD, Standard deviation;

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

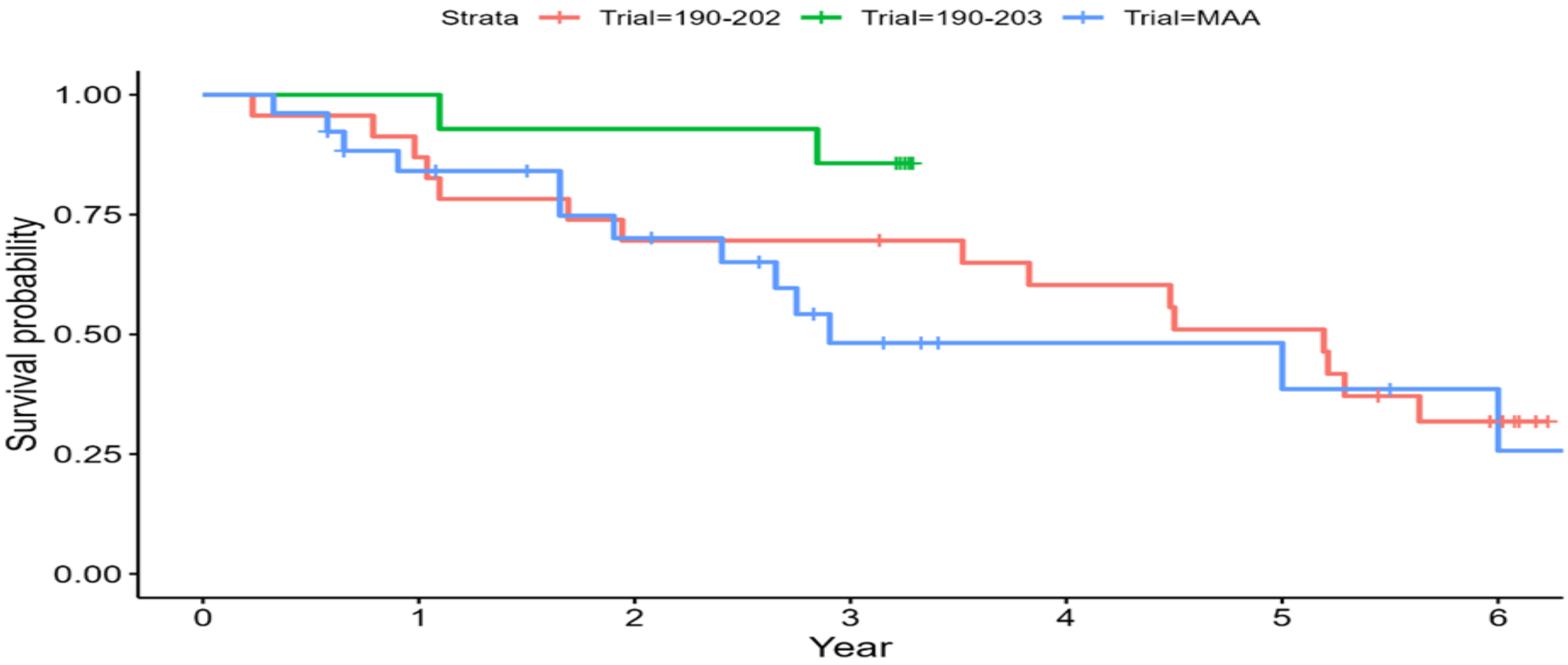
Scenario analyses:

- 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.

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

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

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;