# Highly Specialised Technology

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

# Committee Papers

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**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**HIGHLY SPECIALISED TECHNOLOGY**

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

**Contents:**

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

**First committee meeting:**

1. **Company submission** from BioMarin

2. **Company summary of information for patients (SIP)** from BioMarin

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Batten Disease Family Association (BDFA):
      i. Submission
      ii. Appendix 1 – Family survey
      iii. Appendix 2 – School survey
      iv. Video links

5. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics - York

6. **External Assessment Report – factual accuracy check**

7. **Expert personal perspectives** from:
   a. Paul Gissen, Professor of Metabolic Medicine – clinical expert, nominated by Batten Disease Family Association (BDFA) and BioMarin (company)
   b. Liz Brownnutt, Chief Executive Officer - patient expert, nominated by Batten Disease Family Association (BDFA)
   c. Gail Rich, parent – patient expert, nominated by Batten Disease Family Association (BDFA)
   d. Lucy Carroll, parent - patient expert, nominated by Batten Disease Family Association (BDFA)
   e. Dipak Ram, Consultant Paediatric Neurologist – clinical expert, nominated by Batten Disease Family Association (BDFA) and BioMarin (company)

8. **External Assessment Group cost-effectiveness threshold**

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**analyses excluding disutilities**

9. **External Assessment Report addendum**

**Second committee meeting:**

10. **NICE request to company for additional analysis**

11. **Company additional analysis submission** from BioMarin:
    a. Main submission
    b. Addendum

12. **External Assessment Group critique of company additional analysis**
    12a. Main submission
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**Third committee meeting:**

13. **Company additional analysis submission from BioMarin;**
    a. Additional analysis

14. **External Assessment Group critique of company additional analysis**

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Highly specialised technology evaluation

# Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID6145]

## Document B

## Company evidence submission

**February 2024**

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# List of abbreviations

| Abbreviation | Description |
|---|---|
| ADR | Adverse drug reactions |
| AE | Adverse event |
| AED | Anti-epileptic drug |
| AESI | Adverse event of special interest |
| BDFA | Batten Disease Family Association |
| BNF | British National Formulary |
| CEAC | Cost-effectiveness acceptability curve |
| CeDR | Centre for Disability Research |
| CEM | Cost-effectiveness model |
| CEP | Cost-effectiveness plane |
| CI | Confidence interval |
| CLN2 | Neuronal ceroid lipofuscinosis type 2 |
| CSF | Cerebrospinal fluid |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCA | Data collection agreement |
| DCO | Data cut-off |
| DSU | Decision support unit |
| ECG | Electrocardiogram |
| EEG | Electroencephalogram |
| EEPRU | Policy Research Unit in Economic Evaluation of Health and Care Interventions |
| eMIT | Drugs and pharmaceutical electronic market information tool |
| ERT | Enzyme replacement therapy |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| GOSH | Great Ormond Street Hospital |
| HCHS | Hospital and Community Health Services |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| ICER | Incremental cost-effectiveness ratio |
| ICV | Intracerebroventricular infusion |
| IVT | Intravitreal |
| ITQoL | Infant Toddler Quality of Life Questionnaire™ |
| ITQoL97 | Infant Toddler Quality of Life Questionnaire™ 97-item full-length version |
| ITT | Intent-to-treat |
| KM | Kaplan-Meier |


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| Abbreviation | Description |
|---|---|
| LINCL | Late-infantile neuronal ceroid lipofuscinosis |
| MAA | Managed access agreement |
| MedDRA | Medical Dictionary for Regulatory Activities |
| ML | Motor language |
| MLV | Motor language vision |
| MLVS | Motor language vision seizure |
| MRI | Magnetic resonance imaging |
| mUBDRS | Modified unified Batten disease rating scale |
| N/A | Not applicable |
| N/A | Not applicable |
| NCI | National Cancer Institute |
| NCL | Neuronal ceroid lipofuscinoses |
| NH | Natural history |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NR | Not reported |
| OCT | Optical coherence tomography |
| PASS | Post-authorisation safety study |
| PDCO | Paediatric Committee |
| PedsQL | Pediatric Quality of Life Inventory |
| PedsQL-FIM | Pediatric Quality of Life Inventory – Family Impact Module |
| PRO | Patient reported outcome |
| PSA | Probabilistic sensitivity analysis |
| PSSRU | Personal Social Services Research Unit |
| PT | Preferred term |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| RD-RP | Rare Disease Research Partner |
| RWE | Real-world evidence |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SE | Standard error |
| SEN | Special educational needs |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| SOC | System organ class |
| TEAE | Treatment emergent adverse event |
| TPP1 | Tripeptidyl peptidase 1 |


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| Abbreviation | Description |
|---|---|
| TRE | Temporally related adverse event |
| UK | United Kingdom |
| US | United States |
| VA | Visual acuity |
| VAS | Visual analogue scale |
| WCMC | Weill Cornell Medical College |


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## B.1. Decision problem, description of the technology and clinical care pathway

**Neuronal ceroid lipofuscinosis type 2 (CLN2) is an ultra-rare, progressive, inherited neurodegenerative disease that has a rapid and predictable course of progression from presentation in late infancy to death by early adolescence.**

- CLN2 disease (a form of Batten disease) is caused by pathogenic variants in the *TPP1/CLN2* gene that lead to deficient activity of lysosomal enzyme tripeptidyl peptidase (TPP1). TPP1 deficiency is associated with an accumulation of abnormal lysosomal storage material in neuronal, glial, and retinal cells which leads to neurodegeneration, loss of neurological function, and early death (1-3)
- CLN2 disease has a predictable, rapid course of physical, neurologic, and mental decline that has been observed in cohorts of patients irrespective of gender or ethnicity (2-8)
- CLN2 disease usually manifests in late-infantile children (aged 2–4 years) with seizure onset, typically in combination with a history of early language delay (2, 4-6)
- Disease progression is rapid, leading to the loss of language and walking ability, movement disorders (ataxia, myoclonus, dystonia, and chorea), pain, progressive dementia, and eventual loss of vision, requirement of a feeding tube, and early death (2, 4-6)
- Most children with CLN2 disease become bedridden and blind, dying between the age of eight years and early adolescence; average age of death is ten (2, 4-6)
- CLN2 disease is an exceptionally rare condition (2, 8-10). In England, the estimated number of CLN2 prevalent patients is 40, and approximately five to six new patients are born with CLN2 disease per year (9, 11)
- CLN2 disease deprives the patient of a functional life from early childhood, which has a devastating impact on the quality of life (QoL) of the patient, parents, caregivers, and families (12, 13)
- In addition to the QoL burden, CLN2 disease is associated with severe financial challenges and economic burden for caregivers. Some examples of indirect costs include loss of income as a result of having to care for a child with CLN2 disease, adaptations to homes, specialist care equipment, and travel costs associated with treatment and supportive therapies (12, 13)

**Cerliponase alfa is the first and only technology licensed as a treatment that targets the underlying cause of CLN2 disease.**

- Cerliponase alfa received a positive recommendation by the National Institute of Health and Care Excellence (NICE), and has been available since November 2019 within the context of a managed access agreement (MAA) for cerliponase alfa treating CLN2 (HST12) (14)
- There are currently no alternative treatments licensed or otherwise approved to treat CLN2 disease or the underlying cause of CLN2 disease. Prior to HST12, CLN2 disease management was limited to symptomatic relief and supportive care only, guided by the principles of paediatric palliative care (15, 16)
- Cerliponase alfa, an enzyme replacement therapy (ERT), is an innovative technology that has represented a step-change in the management of CLN2 disease in the UK
- The publication of final results from the pivotal study 190-201/202, spanning 5 years, reveals a significant decrease in the progression of CLN2 disease, as measured by


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the CLN2 Clinical Rating Scale, demonstrating the sustained impact of cerliponase alfa (17, 18).

- Examination of outcomes in the younger patient cohort from Study 190-203 (19-21), where cerliponase alfa therapy was initiated, underscores the sustained high scores in the Motor and Language domains of the CLN2 Clinical Rating Scale. Particularly noteworthy is the absence of any decline in ML scores among early-treated patients over an average observation period of 3 years.
- Healthcare professionals, patient advocates, and families highlight additional benefits of cerliponase alfa in CLN2 disease, encompassing improvements in seizure severity, progressive symptom management, and the overall quality of life for patients, parents, caregivers, and families (12, 13, 22, 23).

### B.1.1. Decision problem

This submission focuses on cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2).

The submission covers the technology's full marketing authorisation for this indication and is consistent with the final scope issued by the National Institute of Health and Care Excellence (NICE).

The UK marketing authorisation for cerliponase alfa in this indication is: *cerliponase alfa is indicated for the treatment of CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency* (24).

Cerliponase alfa received a positive recommendation by NICE in 2019 within the context of a Managed Access Agreement (MAA) for cerliponase alfa treating CLN2 (HST12) (14).

The decision problem for this reappraisal is presented in Table 1.


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**Table 1: The decision problem**

| | Final scope issued by NICE/reference case | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| Population | People with CLN2 | Aligned with scope | N/A, no difference from final scope |
| Intervention | Cerliponase alfa | Aligned with scope | N/A, no difference from final scope |
| Comparator(s) | Established clinical management without cerliponase alfa (including managing the symptoms and complications associated with CLN2) | Aligned with scope | N/A, no difference from final scope |
| Outcomes | The outcome measures to be considered include:<br>• Symptoms of CLN2 including visual function, seizures, myoclonus, dystonia, spasming, pain, and feeding<br>• Disease progression<br>o CLN2 Clinical Rating Scale (reported as 4-domain scale and combined score of the motor and language domains)<br>o Weill Cornell LINCL Scale (4-domain scale)<br>o Hamburg scale<br>• Neurological development which may be informed by measures specified in the MAA for HST12 including Bayley Scales of Infant Development III, WPPSI-IV, Vineland Adaptive Behaviour Scale, and WISC-V<br>• Need for medical care (including hospitalisation, emergency care and primary and secondary care appointments, and concomitant medication)<br>• Mortality<br>• Adverse effects of treatment (including immune response and effects and complications related to treatment administration)<br>• HRQoL (for patients and carers, and including impact on families such as social and mental health and impact on siblings). This may be informed by QoL measures including PedsQL, EQ-5D, and CLN2-QL.Compliance/adherence to treatment | Aligned with scope (see rationale) | Note that the focus of the majority of analyses is based on disease progression, using the CLN2 Clinical Rating Scale; an adapted version of the Hamburg scale (outlined in Appendix M). This submission will focus on the CLN2 Clinical Rating Scale, including a 2-domain (motor and language) subscale called the ML scale.<br>Note that whilst 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. Full details on outcomes reported according to the relevant study are covered in Section B2.4, Table 15<br>The only need for medical care variable collected was seizures that require doctor/hospital visits. No other need for medical care information was |


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| | Final scope issued by NICE/reference case | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | | | collected as part of the clinical evidence. No other differences from final scope. |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. 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. | Aligned with scope where relevant | Cost-effectiveness analysis aligned with reference case. However, 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. |
| Subgroups to be considered | If the evidence allows, the following subgroup should be considered:<br>• Stage of progression of CLN2 | Aligned with scope | Cerliponase alfa is considered to be a relevant treatment for all patients covered by the marketing authorisation. However, scenario analyses are presented in which alternative baseline health state distributions are considered. |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; HRQoL, health-related quality of life; LINCL, late-infantile neuronal ceroid lipofuscinosis; MAA, managed access agreement; MAOG, Managed Access Oversight Group; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life; WISC-V, Wechsler Intelligence Scale for Children fifth edition; WPPSI, Wechsler PreSchool and Primary Scale of Intelligence.


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## B.1.2. Description of the technology

The summary of product characteristics (SmPC) or information for use, and the European public assessment report are provided in Appendix C.

A description of cerliponase alfa is provided in Table 2.

**Table 2: Technology being evaluated**

| | |
|---|---|
| **UK approved name and brand name** | Cerliponase alfa (Brineura®) |
| **Mechanism of action** | Cerliponase alfa is a recombinant form of human TPP1, a lysosomal enzyme, produced in mammalian CHO cells.<br>Cerliponase alfa is an ERT indicated for the treatment of NCL type 2, otherwise known as CLN2 disease or TPP1 deficiency.<br>CLN2 is a type of NCL that is caused by pathogenic variants/mutations in each TPP1/CLN2 gene and that is associated with functional deficiency of TPP1.<br>Cerliponase alfa is an inactive pro-enzyme that is taken up by target cells and translocated to the lysosomes, where it is activated. The activated proteolytic enzyme cleaves tripeptides from the N-terminus of target proteins. Functional deficiency of TPP1 causes CLN2 disease, resulting in neurodegeneration, loss of neurological function and death during early adolescence. |
| **Marketing authorisation/CE mark status** | EMA approval was granted on 30th May, 2017 (25) and UK marketing authorisation was granted on 1st January, 2021 (24). |
| **Indications and any restriction(s) as described in the SmPC** | Cerliponase alfa is indicated for the treatment of CLN2 disease, also known as TPP1 deficiency. |
| **Method of administration and dosage** | Cerliponase alfa is administered to the CSF by infusion via a surgically implanted ICV access device (reservoir and catheter). The ICV access device must be implanted prior to the first infusion. The implanted ICV access device should be appropriate for accessing the cerebral ventricles for the purpose of therapeutic drug administration.<br>Cerliponase alfa must only be administered by a trained healthcare professional knowledgeable in ICV administration in a healthcare setting.<br>Aseptic technique must be strictly observed during preparation and administration. Pre-treatment of patients with antihistamines with or without antipyretics 30 to 60 minutes prior to the start of infusion is recommended. |
| **Additional tests or investigations** | CLN2 disease can be definitively diagnosed either through demonstration of deficient TPP1 activity or through identification of causative mutations in each allele of the *TPP1/CLN2* gene, with most clinicians in the UK and worldwide making the decision to start treatment on the basis of the blood enzyme test only. Thus, no additional tests are required to identify patients eligible for treatment with cerliponase alfa. |
| **List price and average cost of a course of treatment** | List price: £20,107.00 per pack of cerliponase alfa (2x150 mg vials)<br>The recommended dosage† for those over 2 years old is 300 mg every other week (at an annual cost of £522,782 per person). |
| **Patient access scheme** | Cerliponase alfa is available at a cost of £[redacted] per package containing 2x150mg vials, under a confidential PAS discount of [redacted]%. |

Source: MHRA SmPC 2023 (24).
†Based on the cerliponase alfa list price.


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Abbreviations: CHO, Chinese Hamster Ovary; CLN2, neuronal ceroid lipofuscinosis type 2; CSF, cerebrospinal fluid; ERT, enzyme replacement therapy; ICV, intracerebroventicular infusion; NCL, neuronal ceroid lipofuscinosis; PAS, patient access scheme; SmPC, summary of product characteristics; TPP1, Tripeptidyl peptidase I; UK, United Kingdom.

## B.1.3. Health condition and positioning of the technology in the treatment pathway

### B.1.3.1. Disease overview

CLN2 disease is an ultra-rare, severe, neurodegenerative disease that is uniformly fatal. It is an inherited autosomal recessive condition caused by pathogenic variants/mutations in the *TPP1/CLN2* gene that lead to a functional deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1) (1-3). TPP1 deficiency is associated with lysosomal storage material (ceroid lipofuscin), which is normally metabolised by the enzyme, accumulating in neuronal, glial and retinal cells, with progressive degeneration of the brain and retina (1, 3, 26).

CLN2 disease is one of a group of diseases called neuronal ceroid lipofuscinoses (NCLs, collectively known as Batten disease). NCLs are a genetically heterogeneous group of inherited neurodegenerative lysosomal storage disorders, distinguished by their genetic origin, ultrastructural composition of the lysosomal storage material, clinical symptoms, age at disease onset, and course of disease, which are all characterised by the accumulation of ceroid lipofuscin in neurons and other cells. To date, 13 different genes associated with NCLs have been identified (1, 26).

In approximately 85% of cases, CLN2 disease manifests in late infancy (age 2–4 years), with unprovoked seizures and/ or ataxia, often with a history of early language delay (3-5, 27). Atypical CLN2 affects ~10% of patients, who can experience later onset symptoms, a more protracted disease course, and occasionally have a longer life expectancy (10, 28). Atypical cases have been described with more prominent ataxia, less prominent epilepsy, and preservation of visual function, in addition to a slightly longer life expectancy (10, 28). Genotypes from these atypical patients predict reduced, rather than absent TPP1 activity.

Atypical forms notwithstanding, CLN2 disease has a predictable and accelerated course, with rapid loss of motor function and language ability (2, 3), ataxia, movement disorders (myoclonus, dystonia and chorea), progressive dementia, and eventual loss of vision (2, 5, 6) and the ability to swallow (5, 6). The rapid and early clinical decline is most evident after the onset of symptoms, with seizures, language delay, and losses in motor and language functions typically manifesting first, starting at approximately 3 years of age and progressing to limited motor and language function within approximately 2.5 years (4, 5). During this time of rapid progression, children with CLN2 disease can become wheelchair bound and


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dependent on caregivers, and commonly experience respiratory infections and feeding and sleep disruptions (27). Seizures, which can be generalised tonic-clonic, partial, myoclonic, or absence seizures (2, 6, 7), also tend to continue with disease progression and are difficult to treat, often becoming resistant to multiple antiepileptic drugs over time (6, 27).

The majority of children with CLN2 disease become bedridden and blind, and die between the age of 8 years and early adolescence (2, 4-7).

### B.1.3.2. Epidemiology

Evidence for the estimated prevalence and incidence of CLN2 are based on a study by Williams et al, 2011 (9), and clinical practice (11). The exact prevalence and incidence of CLN2 disease is unknown, and it is an exceptionally rare condition (2, 8-10). Based on both sources, in England, five to six children are diagnosed with CLN2 disease each year and approximately 40 children are living with the condition.

Williams et al, 2011 (9) reported that the prevalence of CLN2 disease in the UK was over 0.31 per million of population, with a birth incidence of 0.78 per 100,000 live births. Table 3 presents the data on prevalence and birth incidence of CLN2 disease available in published literature. The 2011 estimates provided by Williams (9) have been provided after consultation with local experts to maximise precision.

**Table 3: Reported prevalence and birth incidence of CLN2 disease**

| Country | Prevalence (per million population) | Birth incidence (per 100,000 live births) | Source | Primary source given, if different |
|---|---|---|---|---|
| Germany | 0.75 | 0.22 | Williams, 2011 (9) | A Schulz, 2008† |
| West Germany | – | 0.46 | Moore et al, 2008 (8) | Claussen, 1992 |
| UK | 0.31+ | 0.78 | Williams, 2011 (9) | Verity et al, 2010 and others |
| Portugal | 0.15 | – | Williams, 2011 (9) | G Ribeiro, 2008† |
| Denmark | 0.54 | – | Williams, 2011 (9) | J Ostergaard, 2008† |
| Sweden | 0.43 | – | Williams, 2011 (9) | Uvebrant and Hagberg, 1997 |
| Norway | – | 0.51 | KSJ Systematic Review in development | Augestad, 2006 |
| Czech Republic | – | 0.36 | Poupetova et al, 2010 (29) | – |
| Netherlands | – | 0.15 | Moore et al, 2008 (8) | Taschner et al, 1999 |
| Italy | – | 0.36 | Moore et al, 2008 (8) | Cardona and Rosati,1995 |
| Canada (Newfoundland) | – | 9 | Moore et al, 2008 (8) | – |


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| Country | Prevalence (per million population) | Birth incidence (per 100,000 live births) | Source | Primary source given, if different |
|---|---|---|---|---|
| Oman | – | 4.9 | Al-Maawali et al, 2012 (30) | – |
| Argentina | 0.1 | – | Williams, 2011 (9) | Noher de Halac, 2008† |

Source: Williams et al, 2011 (9).
May include variant cases of late infantile NCL, especially for birth incidence, as many studies precede availability of molecular diagnostic tests.
†Personal communication (9).
Abbreviations: NCL, neuronal ceroid lipofuscinoses; UK, United Kingdom.

The range seen in the literature is thus 0.10–0.75 per million for prevalence and 0.15–0.78 per 100,000 live births for incidence, if obvious outliers in small, highly consanguineous populations (such as Newfoundland and Oman) are excluded. These data are consistent with the worldwide prevalence of 0.6–0.7 per million and worldwide incidence of 0.46/100,000 live births stated by Chang et al, 2011 (2).

Based on the Williams et al study and an estimated worldwide prevalence of 0.75 per million population, incidence of ~0.5 per 100,000 live births, a total UK population of 67 million people, and 605,479 live births per annum in England and Wales (31), the number of CLN2 prevalent patients would be in the order of 50, with an estimated three new patients born with CLN2 disease per year in England and Wales.

In England, real world clinical and patient expert data shows that in recent years five to six children are diagnosed each year and currently around 40 children are living with the condition (11). Between November 2019 and September 2023, 26 new patients were diagnosed in England and enrolled in the MAA, equating to ~6.5 patients diagnosed per year (11). Since the epidemiology estimates are based on identified cases, and as access to paediatric neurologists and medical genetics is limited, it is likely that there are additional cases that remain undiagnosed.

### B.1.3.3. Course of CLN2 disease

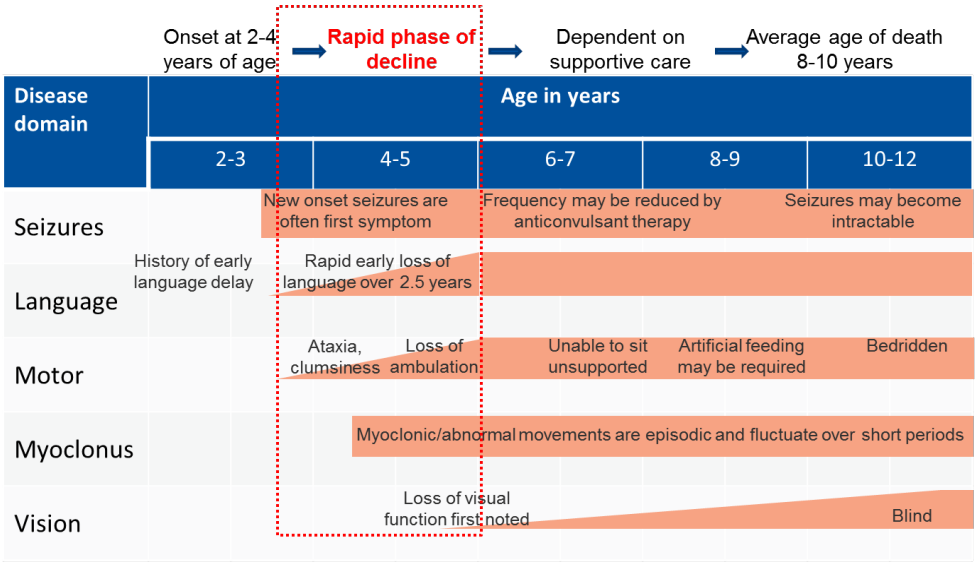
As presented in Figure 1, a very consistent and predictable time course of CLN2 disease progression can be described (2, 4-6):

- Seizure and ataxia onset occurs around the age of 2–4 years, and may be preceded by a history of delayed speech.
- There is a rapid parallel decline in motor function and language ability, starting around 3 years of age with complete loss of function over the course of 2.5 years.


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- Limb spasticity, truncal hypotonia and loss of head control lead to complete loss of independent mobility between the ages of 4 and 6 years.
- Most patients are unable to sit unsupported by the age of 6 years.
- In addition to losing motor function and speech, patients will start to suffer myoclonus, dystonia, and severe spasticity, causing pain and distress, from the age of 4 years.
- A decline in visual ability can occur from approximately 6 years of age, when progressive psychomotor disturbances have already become obvious, leading to blindness within about 3 years.
- Most children lose the ability to swallow, which may lead to the use of nutritional support through a nasogastric or gastrostomy tube.

**Figure 1: Typical course of CLN2 disease**




As can be seen in Figure 1, CLN2 disease is considered a disease of childhood dementia, which remains undetected for the initial years of life, suddenly manifesting and depriving the patient of a functional life from late infancy. This consequently has a devastating impact on the quality of life (QoL) of parents, caregivers and families (12), described in more detail in Section B.1.3.4.2.

A number of publications have described aspects of the time-course of disease progression in cohorts of patients with CLN2 disease (3-5, 7, 8). The level of detail of reporting on different features of the natural history (NH) varies considerably between publications; however, there is remarkable consistency between publications on the timing of onset of


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CLN2 symptoms, with a distinct, predictable, and rapid course of decline, irrespective of ethnicity or gender (3-5, 7, 8).

In order to evaluate disease progression clinically, the Hamburg scale is validated to assess the regression of motor and language function as well as seizures and vision. The Weill Cornell LINCL scale is an adapted version of the Hamburg scale, which includes the categories swallowing and myoclonus instead of seizures and vision. Both scales have been combined and definitions of scores edited to be used as efficacy measures in clinical trials, such as the CLN2 Clinical Rating Scale used in the trials presented in HST12, as well as this appraisal. The CLN2 Clinical Rating Scale of motor (M), language (L), vision (V), and seizure (S) function facilitates the quantification of clinical progression, with each function evaluated on a scale of 0–3 to give a total combined score between 0 and 12, with lower scores representing more advanced disease. As loss of motor and language function are the primary symptoms of CLN2 disease progression, a subscale of the CLN2 Clinical Rating Scale, the 0–6 scored ML Score, comprising of the respective domains, is often employed to assess disease progression. The Hamburg, Weill Cornell LINCL, and CLN2 Clinical Rating Scales are described further in Appendix M.

### B.1.3.4. Disease burden

#### B.1.3.4.1. Clinical burden

Prior to the positive recommendation of cerliponase alfa as a result of HST12, CLN2 disease management was restricted to symptom management and supportive care only, with a wide range of drugs used in the management of CLN2 symptoms and palliation. Notably, none of these drugs address or have an impact on the underlying cause of the disease, namely, the defective genetic mutation(s).

Multiple antiepileptic drugs and muscle relaxants are used for the treatment of seizures and movement disorders, symptoms experienced by most patients. It is also common to use analgesic medication for pain of different origins, and inhaled anti-muscarinic drugs to reduce secretions, used alongside non-pharmacological therapies and interventions.

In a survey in the UK and Germany, caregivers reported that children were prescribed a large number of medications to manage their symptoms, which included seizures, secretions, twitchiness/dystonia, mood changes, difficulty sleeping and problems associated with lack of mobility, vision, and communication (12). Due to the many different medical, practical, and psychosocial needs of patients and families, a multidisciplinary team approach is required to manage CLN2 disease. Experts listed many different types of health and social


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care professionals who are involved in the care of their patients, as shown in Table 4 (15). In many cases, there is also the need for one parent to give full-time commitment as primary caregiver (32-34).

**Table 4: Multidisciplinary care expert list for patients with CLN2**

| Neurological disease specialists | Other medical specialists | Therapists to optimise function | Family/Social |
|---|---|---|---|
| • Neurologist/ paediatric neurologist<br>• Neuro-disability expert<br>• Neuro-developmental therapist<br>• Neuromuscular specialist | • Cardiologist<br>• Gastroenterologist<br>• Ophthalmologist<br>• Paediatrician<br>• Pulmonologist<br>• Pain therapist | • Feeding therapist<br>• Dietitian<br>• Physical therapist<br>• Speech therapist<br>• Sleep therapist | • Genetic counsellor<br>• Home nursing<br>• Palliative care team<br>• Social worker<br>• Psychologist |

Abbreviation: CLN2, neuronal ceroid lipofuscinosis type 2.

A key clinical problem is the highly specialised nature of the care and management required, which is confounded by the rare nature of CLN2 disease. This means that only a small number of very specialised centres and healthcare professionals have experience in managing this rare condition.

Since HST12, in addition to Great Ormond Street Hospital (GOSH), Birmingham Children's Hospital, Bristol Royal Hospital for Children, Manchester University Hospital, Royal Victoria Infirmary Newcastle, and Salford Royal Hospital have all become specialist centres for the administration of cerliponase alfa for patients with CLN2 disease. With more centres providing CLN2 disease treatment travel times, expenses, and travel-related stress for caregivers and families of patients with CLN2 disease have all reduced (13).

**Mortality**

Table 5 presents mortality evidence based on NH data for patients with classical onset CLN2 disease, which shows an average age of death between 8 and 12 years, with few patients surviving into teenage years.

The median age of death of 10.1 years in the DEM-CHILD database cohort (Nickel et al, 2018 (4)) is based on 20 patients for which the date of death was known. An estimated age of death was calculated for an additional 66 patients for whom vital status and date of last follow-up was known. Using Kaplan-Meier (KM) analysis to predict time to death following last assessment, the predicted median time from first symptom to death was 7.8 years. With


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a median age of first symptom of 2.9 years, the combined median age at death of 10.7 years is consistent with that observed in the smaller sample.

**Table 5: Natural history age of death for patients with CLN2 disease**

| Author, year (Ref) | Age (years) at death | Comment |
|---|---|---|
| Nickel et al, 2018 (4) | Median: 10.1<br>SD: 3.2 | Median (SD) age at death for the 20 patients for which date of death known.<br>Date of last assessment used as censoring date when date of death not known for KM analysis of time from first symptom to death: Median 7.8 years (n=66) |
| Moore et al, 2008 (8) | Median: 8.6<br>Range: 4.0–12.9 | Median (range) for 27/28 patients who died during the study |
| Steinfeld et al, 2002 (5) | Range: 5–11 | Age range at death for the 'standard' patients with common mutations who died during the study (unknown number out of 16 patients) |
| Sleat et al, 1999 (35) | Median: 9.0<br>SD: 2.45 | Median and SD calculated for the 22 patients with late-infantile onset who were dead at time of report.<br>Publication reports 'lifespan >8.3±2.8' for 43 patients (including those still alive). |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; KM, Kaplan-Meier; MAA, managed access agreement; SD, standard deviation.

Three deaths in cerliponase alfa treated participants have been reported across the clinical evidence presented in this appraisal; [redacted], two deaths occurred in cerliponase alfa treated participants in two long-term observational safety studies (see Section B.2.10.1 for more details). However, no expectation of extra-neurological mortality was associated with cerliponase alfa treatment, which is indicative of a decreased overall mortality risk and increased survival.

#### B.1.3.4.2. Quality of life burden

CLN2 disease exhibits a predictable and rapid course of decline which deprives the patient of a functional life from early childhood, and consequently this disease has a devastating impact on the QoL of patients, as well as parents, caregivers, and families (12, 33).

**Impact of CLN2 on health-related quality of life**

The health-related quality of life (HRQoL) of patients with CLN2 disease has been compared with that of the US general population using the infant toddler quality of life (IT-QoL) questionnaire (36), a well-validated HRQoL measure used with parents of children aged between 2 months and 5 years. This was studied in 18 patients with CLN2 disease in the Weill Cornell Medical College (WCMC) clinic aged between 2.5–11.0 years who were untreated with cerliponase alfa (18). The items of each domain were summed and


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transformed into their respective scores on a 0–100 continuum that ranges from 0 (worst possible score) to 100 (best possible score) according to the standard scoring procedure. Results are shown alongside those of the United States (US) general population in Table 6.

A difference of five points or more in the IT-QoL total or domain scores is considered to be clinically meaningful. CLN2 patients had much lower HRQoL scores than the general population that were clinically meaningful on most domains, with the clear exception of family cohesion and bodily pain/discomfort (18).

**Table 6: Comparison of HRQoL of CLN2 patients vs general population on the IT-QoL**

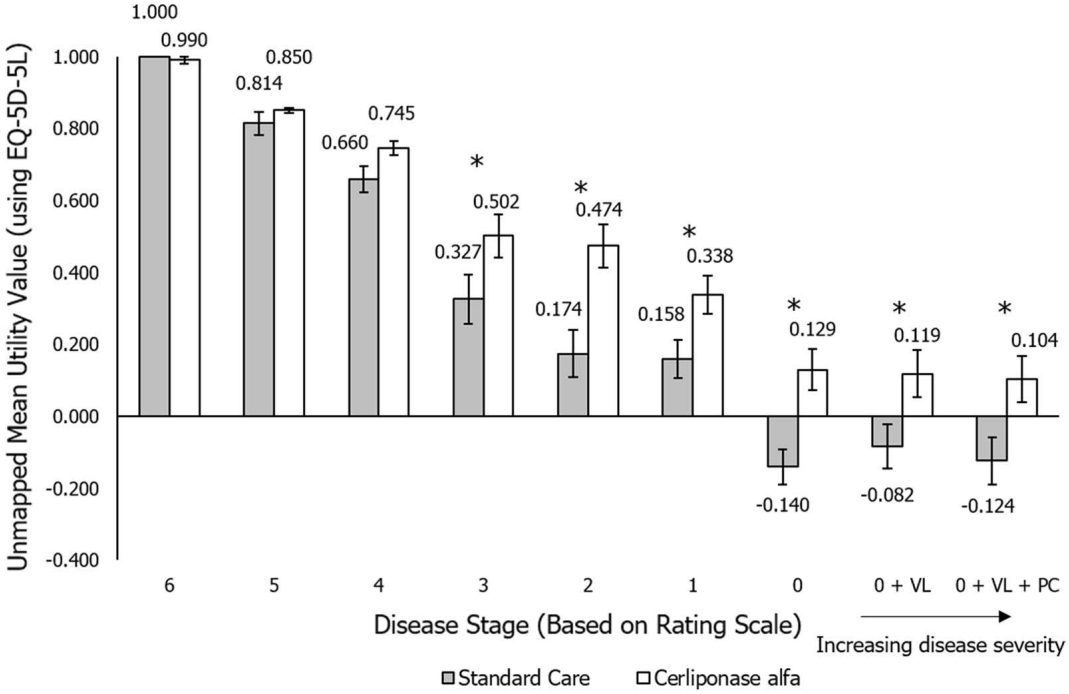
| IT-QoL Domains | Mean score (SD) | | | |
|---|---|---|---|---|
| | CLN2 patients (n=18) | US general population (n=410) (36) | Difference in mean | Effect size – cohen's d |
| Growth and development | 48.0 (15.3) | 86.5 (10.6) | –38.5 | –2.9 |
| Physical abilities | 58.8 (21.8) | 97.2 (9.8) | –38.4 | –2.3 |
| Parental emotional impact | 43.8 (23.2) | 92.1 (10.5) | –48.4 | –2.7 |
| General health | 52.2 (8.7) | 79.0 (14.5) | –26.8 | –2.2 |
| Behaviour | 50.5 (9.4) | 71.4 (8.8) | –20.9 | –2.3 |
| Parental impact time | 53.4 (32.0) | 93.0 (11.0) | –39.6 | –1.7 |
| Change in health | 20.1 (24.7) | 56.1 (18.4) | –36.0 | –1.7 |
| Temperament and moods | 67.9 (10.0) | 77.2 (10.5) | –9.3 | –0.9 |
| General behaviour | 61.5 (25.4) | 72.8 (12.7) | –11.3 | –0.6 |
| Global behaviour | 50.5 (9.4) | 71.4 (8.8) | –20.9 | –2.3 |
| Bodily pain/discomfort | 87.7 (13.8) | 83.8 (16.8) | 3.9 | 0.3 |
| Family cohesion | 78.1 (23) | 75.3 (18.8) | 2.8 | 0.1 |

Source: BioMarin, 2016 (Data on file) (18).
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; HRQoL, health-related quality of life; IT-QoL, infant toddler quality of life; SD, standard deviation; US, United States.

As there are no published utility data fully capturing all CLN2 disease stages, a recent case study employed an indirect elicitation method using proxy-reporting by clinical experts (37). This case study demonstrated how utility values can be estimated for ultra-rare paediatric diseases by asking clinicians to complete EQ-5D-5L questionnaires based on vignettes describing the individual stages of CLN2 disease. Utility values for vignettes were based on the EQ-5D-5L responses from the eight participants. Vignettes, describing all nine disease stages for both patients treated with standard care and those treated with cerliponase alfa, were obtained using the UK value set. In patients with a ML score of 6 (the least impaired disease stage) utility values for patients receiving cerliponase alfa were equivalent to perfect health; mean standard error [SE] value of 1.000 (0.000), compared with mean (SE) values of 0.990 (0.010) on standard care treatment (Figure 2). Utility values then decreased in both treated and untreated subjects, as the vignettes described increasingly more progressed stages of disease.


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**Figure 2: Mean utility values across CLN2 disease stages using the unmapped EQ-5D-5L value set**




Source: Gissen et al, 2021 (37)
Mean values ± 1 SE are shown on the chart. Utility values are given on a scale where 1 is equivalent to perfect health, and 0 equivalent to death. UK value set. Asterisks (*) indicate a statistically significant difference between treatment with standard care and cerliponase alfa using a paired t-test, $p < 0.05$..
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; EQ-5D-5L; EuroQol-5 Dimension 5 Levels; PC, palliative care; SE, standard error; VC, vision loss.

Analysis of the individual dimensions of the EQ-5D-5L showed that the greatest differences between patients treated with cerliponase alfa and those receiving standard care occurred in the pain dimension (differences in mean scores ranged between 0 and 1.8), with notable differences also observed in the anxiety/depression dimension (differences in mean scores ranged between 0.1 and 1.0) (37). Exempting ML score 6, vignettes describing patients receiving cerliponase alfa were consistently assigned higher utility values for the same disease state, suggesting this treatment improves HRQoL compared with standard care (37).

### Impact of CLN2 disease on caregivers and families

The journey through the diagnosis, clinical assessments, treatment, and management of CLN2 disease patients has a profound impact on family life. Historically diagnosis often comes after a protracted and emotionally challenging journey of two or more years, placing a significant burden on families. At the moment of diagnosis, families not only grapple with the medical aspects but also receive information, relevant resources. Advocacy groups become a vital support network for family members, acknowledging the emotional toll (16). Palliative care teams play an essential role, customising their involvement based on individual needs and available resources. The comprehensive approach extends to offering genetic


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counselling and family planning services (16). Ongoing grief and bereavement support are integral components, accompanied by encouragement for families to engage in memory-making activities (38). The multifaceted challenges faced by families underscore the importance of holistic and supportive care in navigating the complexities of CLN2 disease.

A study by Schulz et al, 2020 examined the burden of CLN2 disease in a survey of 19 families in the UK (n=9) and Germany (n=10), based on home surveys and focus groups. This study demonstrated the wide-ranging challenges of caring for and living with a child with CLN2 disease, as well as the severe impact of CLN2 disease on caregivers, siblings, and families as a whole (12). These impacts were validated during a July 2023 advisory board with patient advocates, a group which included three parent representatives who have at least one child enrolled in the MAA cohort (13). The impacts reported include:

- **Physical, emotional, and psychological impact on caregivers and families**

  Caring for a child with CLN2 disease has a significant impact on family life, including having to share tasks between caregivers and upheaval of routines. Caregivers reported that caring for a child with CLN2 disease was overwhelming; one described it as “a full-time job for three people”. Sleep disruption, back pain due to carrying the affected child, anxiety/depression, and exhaustion were all reported, as well as difficulties in looking after one’s own health while providing care (12). This was validated by patient advocates who all agreed that the day-to-day care burden is extensive, with some patients requiring 24/7 all-round care (13). For instance, patients with progressed disease not only require help with going to the toilet, feeding, and washing, but also help using splints, and help with mobility. Parents described having very limited time for themselves and for their partners, as far as not having enough time “for a cup of coffee together”. The more progressed the disease becomes, and the larger the child grows, the more complex the patient care becomes. This more complicated care requires increased training and strength, making it difficult to ask friends/family to step in and alleviate some of the care duties.

  Caregivers reported the difficult emotional impact of caring, which meant they felt sad but had to “deal with their situation”. Families reported that the journey to establishing a correct diagnosis could take as long as two years, resulting in feelings of anger and frustration. In addition to the enormous emotional burden on families, primary caregivers reported spending 96 hours providing care in a usual week and typically sleeping for as little as five hours per night (12). Patient advocates, and especially parent representatives, also reported a large impact on caregiver mental health, describing feelings of isolation; having limited time for themselves; and anxiety for the future,


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including worries that access to cerliponase alfa for their child or children may be withdrawn in the future (13).

- **Impact on family relationships**

  Several families reported an impact on their family relationships, with some family members distancing themselves following a child's diagnosis, while other families became closer (12). An impact on siblings was also reported, with some parents reporting that it was often difficult for the unaffected sibling to understand what was wrong with the affected sibling (12). Caregivers also reported finding it difficult to share time and attention between children. The external support families received varied, with one caregiver reporting being very isolated, and other families saying they had help from friends and family (12).

  The impact on siblings is profound and deep, with siblings experiencing psychological effects and major anxieties (13). Advocates gave two examples of children they were aware of whose mental health had significantly been impacted. One child required play therapy, which established that they were angry at the disease and grieving for their sibling. The other child was diagnosed with post-traumatic stress disorder as a result of witnessing their sibling's resuscitation following a seizure. Siblings' relationships with their parents are also impacted, as they have reduced time to spend together due to the parents' caring responsibilities, and parents reported having to work extra hard to maintain these relationships. Patient advocates noted that the worries that siblings have shown include anxieties towards their affected sibling; towards whether they might develop CLN2 disease themselves in the future; and whether they may be carriers of the genetic mutations responsible for CLN2 disease (13).

- **Financial impact**

  Families described the financial impact of caring for a child with CLN2 disease, which included giving up work to provide care or being unable to return to work, having to take time off from work, incurring additional expenses, applying for benefits, and waiting for funding. During discussions, there were reports of caregivers having to give up work to care for their child and one caregiver described not being able to find work having been out of the labour market for a while due to caregiving (12).

  Secondary caregivers of patients with CLN2 disease reported the greatest work impact (33). Work Productivity and Activity Impairment showed that secondary caregivers had greater impact on their work (in terms of absenteeism, and presenteeism) compared to


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primary caregivers (33). Secondary caregivers also exhibited notable levels of productivity impairment and work/activity impairment to a level comparable with caregivers of cancer patients (unmatched controls from the EU National Health and Wellness Survey) (33). The financial burden of CLN2 disease can be severe, mainly driven by loss of or reduced employment-related income, as well as the necessity to self-fund the healthcare needs of the child, including care equipment and adaptations to homes and cars (12). During the advisory board, patient advocates highlighted the financial burden of caring for patients with CLN2 disease (13), noting the costs of specialist wheelchairs, home installation of hoists and ramps, and orthotics (including daytime and night-time splints) (13).

A survey in the US and Canada of parents of patients with NCLs, a third of whom had CLN2 disease, reported very similar qualitative findings (32).

- **Education**

  Education for children with CLN2 disease remains important, particularly as an exercise that is both socialising and stimulating. All the affected children from families participating in the Schulz et al, 2020 study focus groups were or had been in education, except for one child from Germany, and most of them were attending special needs schools where they received one-to-one support throughout the day (12). However, many caregivers had experienced considerable difficulties and frustrations in obtaining access to these schools or access to the support the child needed to manage mainstream school during the period when they did not have a clear diagnosis, even though the children undoubtedly needed specialist support.

  As of the most recent update (February 2024) on participants in Study 190-203 (19), it is noteworthy that 3 of the patients who received early treatment before the age of 2 are currently participating in mainstream education. This positive development underscores the potential long-term benefits of early intervention and merits special consideration in our discussions.

  Patient advocates from England noted that options for education were dependent on the child's stage of CLN2 disease progression and on when the child started cerliponase alfa treatment, with them either attending a mainstream or special needs school or being home schooled (13). The impact of CLN2 symptoms such as changes in vision, language, and mobility all negatively affect patients and their ability to attend school and were reported to be more severe when cerliponase alfa treatment was initiated at a later CLN2 disease stage.


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- **Social impact and isolation**

  The social support received by surveyed families varied considerably, with some respondents reporting feeling isolated, while others derived a lot of support. Experiences ranged from lacking family support and frequent feelings of extreme loneliness through to receiving ongoing help from extended family, friends, schools, and community groups. One caregiver described feeling very isolated, as they were a single parent and had no family to help. They said they felt as though they “had to beg people” to help them push wheelchairs into town and had given up trying to go out (12).

  Some surveyed families reported opting for selective terminations when they found out their pregnancy was affected by CLN2 disease and having other siblings genetically tested (12). A few caregivers discussed the impact of understanding the course of the disease and their hopes that their child would live as long as possible. When describing positive impacts of caring for a child with CLN2 disease, one caregiver reported having learnt a lot from other families in similar situations, and a few caregivers reported a change in their outlook on life and learning not to worry and be appreciative of life. This was validated during the patient advocate advisory board, where parents described the positive outlook that caring for patients with CLN2 disease had given them, noting that they ‘live in the moment’ more and that their caring responsibilities had given them a ‘better outlook on life’ (13).

  Schulz et al, 2020 assessed the QoL of families caring for a child or children with CLN2 disease using the EQ-5D-5L, the Pediatric Quality of Life Inventory (PedsQL) Parent Report for Toddlers and the PedsQL Family Impact Module (PedsQL-FIM) instruments (12). Disease stage (rapidly progressive, late, and deceased) had a strong impact on caregiver burden; caregivers of children in the late stage of CLN2 disease reported a greater number of hours caring and less sleep than both caregivers of children in the early/decline stage. Overall happiness reduced with disease stage, but life satisfaction was broadly similar across stages. QoL was considerably lower in the late disease stage than the deceased stage; the rapidly progressive stage fell between the two extremes. PedsQL-FIM scores were lowest for families with a child in the late stage of CLN2 disease for all domains except family relationships.

  Across other health and wellbeing measures, caregivers (UK and German caregivers combined) reported significantly lower life satisfaction and lower happiness with their partner; an average of 73.4 more caring hours per week; and 1.3 fewer hours sleeping per night, compared with parents with a non-sick or disabled child of the same age (12).


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Ultimately, families caring for a child affected by CLN2 disease must cope with many difficult emotional, physical, professional, financial, and logistical challenges.

**Impact of cerliponase alfa on quality of life burden**

Although there are no published data on the specific impact of cerliponase alfa on QoL burden, first-hand experiences were captured during both the patient advocate and healthcare professional advisory boards conducted in July 2023 (13, 39).

- **Cerliponase alfa treatment – Quality of life impact on patients with CLN2 disease**

  Patient advocates and healthcare professionals all verified that children diagnosed in the early stages of CLN2 disease and treated with cerliponase alfa had better outcomes than children receiving standard of care (SoC). Healthcare professionals agreed that the risk of death would also differ between patients being treated with cerliponase alfa vs SoC, noting that as the risk of seizures reduces with cerliponase alfa treatment, so do comorbidities that are caused by seizures (39).

  Patient advocates with more than one affected child had first-hand experience of observing the outcomes of children diagnosed and started on treatment at different ages and stages of disease progression. They stressed that the difference in outcomes between siblings diagnosed at different times in the disease pathway inferred how transformative treatment with cerliponase alfa has been. They emphasised that the differences between patients that start treatment earlier vs later in the disease progression is ‘undeniable’, with one parent noting that their child who started treatment early has a normal, healthy, and active life, going to mainstream school and partaking in activities such as riding a bike and ballet, whilst their child who was diagnosed and started on cerliponase alfa treatment later is fully dependent on 24/7 care. Another advocate with two affected children stated that their younger child is doing well and “almost like a normal healthy child”; in contrast, though the older sibling is in a stable condition and no longer regressing, they are fully dependent on parental care (13).

- **Cerliponase alfa treatment – QoL impact on caregivers and families**

  Parents on the patient advocate advisory board with a child/children with CLN2 disease treated with cerliponase alfa noted that their QoL as caregivers and as a family unit had improved with availability of treatment, due to the increased time that cerliponase alfa has allowed them to spend together as a family, as a result of disease stabilisation (13). One parent stated that the reduced frequency of seizures experienced by their two children with CLN2 disease since starting cerliponase alfa treatment had significantly


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improved their family's ability to leave the house. Before starting treatment, the parent described not wanting to take their child out on their own due to the risk of seizures at the playground and the worry that the child may fall off equipment and hurt themselves. Going on short excursions or simply leaving the house to be in the garden with a child with CLN2 disease was reported to be highly time consuming, requiring a substantial amount of preparation time, with one advocate describing it as an 'absolute marathon'. One patient advocate noted that a reduction in seizures allows families to go out and engage in more normal activities, such as walks, as well as going on holiday. Improvements in seizure frequency/severity allowed families to engage in more normal activities, to plan more generally, and to 'look ahead'. Patient advocates stated that their QoL was therefore significantly improved. In general, parents at the patient advocate advisory board noted that they had a better outlook on life as a result of cerliponase alfa availability (13).

Overall, the results presented by Schulz et al, and the advisory board can be interpreted as a stabilisation in QoL with cerliponase alfa treatment of CLN2 disease. Consulted experts consider this stabilisation as beneficial, compared with the considerable QoL deterioration experienced with non-stabilised disease (39).

#### B.1.3.4.3. Economic burden

Families caring for a child affected by CLN2 disease have to cope with many difficult emotional, physical, professional, logistical, and financial challenges. Some families have more than one affected child, leading to an even greater burden (33). These challenges are typically endured from before diagnosis and continue to the point of and after the child's death, leaving a long-term familial legacy of emotional distress, poor health, and financial strain.

Later, more advanced CLN2 disease is associated with more intensive medical needs and greater healthcare resource use, including more frequent appointments with specialist clinicians, nurses, and therapists. Other costs, such as seizure-related costs (e.g. medications and hospitalisation), also increase as the patient's disease progresses.

The financial burden of caregiving for a child or children with CLN2 disease is significant – caregivers often must work reduced hours or give up work completely in order to care for their child. Additionally, in the UK, 36% of families with an affected child were reported to have bought a more accessible property and 50% moved to a more accessible property, both of which were self- or family-funded (12). Furthermore, 50% of the overnight accommodation costs during hospitalisations of an affected child were self- or family-


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funded (12). During the patient advocate advisory board, one parent reported having to work in the evening and where they could during the day due to the time-consuming caregiving required from them (13). The personal financial implications were reported to be enormous by all advocates.

In the UK, families with one or more children affected by CLN2 disease are eligible for financial assistance and support from other government departments; this can relate to the care for their affected child, other non-affected children, or to support parents (33). Most primary caregivers reported receiving a reduction on their council tax, as well as receiving additional school support paid for by their local education authority and a blue disability badge for parking (33). The physical and emotional burden for families applying and navigating the benefits systems is high, and they rely on support from organisations such as the BDFA to help and advocate on their behalf.

The indirect financial costs typically borne by patients, their caregivers, and families, and that are not reimbursed by the NHS include:

- **The cost of adaptations to the home, adaptive appliances, and other care equipment**

  The cost of home adaptations (e.g. the addition of home extensions, lifts, wheelchair ramps, and grab rails) and extra equipment to look after an affected child (e.g. wheelchairs, sleep systems) is considerable. For example, home adaptations can cost up to £30,000; specially designed wheelchairs up to £3,000; and adapted cars up to £10,000 (personal communication, BDFA).

  Grants and funding are rarely available to meet the costs of adaptations and equipment; where funding has been available, caregivers frequently report long waits to receive it, which is extremely stressful and increases their care burden. Families described the stress and frustration of having to wait for long periods (in some cases, many months) while funding decisions were made and requests for equipment or adaptations processed (33).

- **Loss of income as a result of having to stop working to care for a child with CLN2 disease**

  During patient advocate advisory board discussions, families described the financial impact of caring for a child with CLN2 disease, which included taking time off from work


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or giving it up entirely to provide care, or difficulties returning to work following a period of caregiving (13).

A study by the US Batten Disease Support and Research Association (BDSRA) included a survey of 93 parents and caregivers (aged 25–71 with 70% (n=65) aged 35–55 years; 86% (n=80) female; 95% (n=84) Caucasian) of children with Batten disease (33% of those with CLN2 disease) (32). Concerns related to finance were similar to those in the UK. Financial issues arose from making the family home and vehicle accessible for affected children. Most (68% (n=63)) caregivers reported having to leave their job because of their child's diagnosis; 86% (n=80) reported a negative change in household income since diagnosis; and 55% (n=51) felt their current income did not meet family needs (32).

- **Cost of transportation to and from hospital to access management and care services, parking charges, and overnight accommodation**

  Families need to travel to every hospital appointment, which involves journey times and transportation costs for the family that build up over time, with some journeys also involving overnight stays. Since the availability of cerliponase alfa in England, the increased number and geographical spread of specialist centres has improved access to treatment and decreased the associated costs of travel. Reduced travel has not only led to financial savings but also improved family QoL, continuity of education, and sibling well-being (13).

### B.1.3.5. Clinical pathway of care

#### B.1.3.5.1. Clinical guidelines

There are currently no UK national guidelines or guidance in place for the management of CLN2 disease, despite the availability of cerliponase alfa treatment for the treatment of CLN2 disease under the MAA (HST12). The purpose of this agreement was to describe the uncertainties identified by NICE's technology appraisal committee, patient eligibility criteria, and arrangements intended to capture the data that may address these uncertainties.

In 2015, 24 disease experts (healthcare professionals and patient advocates) from eight countries, including the UK, completed a survey comprising questions on CLN2 disease management, and a subset subsequently met to discuss management practices (15). Their work represented an important first step towards development of consensus-based expert professional management guidelines for CLN2 disease. In 2021, 21 disease experts (healthcare professionals and one patient advocate), including three UK experts, developed


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guidelines on the diagnosis, clinical assessment, treatment and management of CLN2 disease patients (16). These guidelines consist of 53 statements, with the aim of providing a basis for adaptation to local policies and healthcare systems (16).

#### B.1.3.5.2. Diagnosis of CLN2 disease

Early diagnosis of CLN2 disease is critical to ensure optimal care for patients and families; but it is challenging, primarily due to a lack of disease awareness within the clinical community and the non-specificity of initial presenting symptoms.

Diagnosis of CLN2 disease is based on laboratory testing following clinical suspicion (10). To confirm a clinical suspicion of CLN2 disease, the recommended gold standard for laboratory diagnosis is the 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 (10, 16).

Specific polyclonal antibodies against TPP1 detect the absence or marked reduction of this protein in lymphocytes, lymphoblasts, fibroblasts and brain homogenates from patients, a technique found to be accurate, cost-effective, and rapid (16).

There are a limited number of circumstances when it may be necessary to use a second method to obtain a diagnosis; for example, if *CLN2* genotyping finds only one mutation or a variant of unknown significance. When it is not possible to perform both analyses, either demonstration of deficient TPP1 enzyme activity in leukocytes or fibroblasts, or detection of two pathogenic variants in *trans* is diagnostic for CLN2 disease (10).

**Challenges in gaining a CLN2 disease diagnosis**

The diagnostic workup of isolated language delay in an otherwise “normal” toddler is limited once hearing loss is ruled out, and gaining control of seizures may take precedence over determining their aetiology, contributing to delays in diagnosis. In addition, symptoms such as ataxia may initially be misinterpreted as side effects of anticonvulsive medication (15). A delay of two to three years between symptom onset and diagnosis of CLN2 disease is common, and some children may appropriately be referred for speech therapy or have treatment for epilepsy prior to further investigation of symptoms (13, 16, 34, 39).

The delay and challenges in gaining a CLN2 disease diagnosis were validated by healthcare professionals experienced in treating patients with CLN2 disease during a July 2023 advisory board (39). Advisers emphasised a lack of disease awareness, especially amongst general practitioners and paediatricians, who are generally the first point of contact for


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families. Delays in diagnosis can occur because healthcare professionals do not consider CLN2 disease based on initial patient symptoms. For instance, seizures – often an early and detectable CLN2 symptom – are not always recognised for their clinical significance and therefore not always appropriately investigated, further delaying diagnosis (39).

The effect of the COVID-19 pandemic is anticipated to be a factor that may still be affecting the extent of disease progression at diagnosis, with some children potentially yet to be diagnosed as a direct impact of pandemic-related clinical delays. Validated by clinician advisors, the full fallout of the pandemic is still to be seen, which is a pattern that has also been observed for other rare conditions treated at GOSH (39).

It is anticipated that greater clinical awareness could result in earlier diagnosis, as demonstrated by a recent manufacturer-led programme in the US targeted at diagnosing the underlying genetic cause of seizures in children. The programme resulted in a decrease in time-to-diagnosis of CLN2 disease, with cases diagnosed significantly earlier than was previously the typical case for this disease (average time from first symptom [9.8 vs 22.7 months; $p<0.001$]) (34, 40). Facilitated access to early epilepsy gene panel testing helped to increase diagnostic yield for CLN2 disease, shortening time to diagnosis and enabling earlier intervention.

BioMarin has sponsored a diagnostic program through a third-party laboratory (Blueprint Genetics) in 54 European and Middle-Eastern countries since 2017 (41). This program involves a comprehensive epilepsy panel designed to molecularly test and diagnose 511 genetic epilepsy-related diseases in patients aged 24 to 48 months. From November 2017 to December 2022, with full results available for the last year, 1088 samples were collected across 31 countries (41). Out of these, only 19 cases of CLN2 were diagnosed, emphasising the ultra-rare nature of TPP1 deficiency (diagnostic yield 1.7%) (41). It is noteworthy that over the six years of the program, the average age of confirmed diagnoses for the 19 cases decreased from 46 to 47 months (2017-2020) to 38 months (2021) and further to 37 months (2022) (41). In the original evaluation of cerliponase alfa, the responsibility for enabling access to these diagnostic approaches was assigned to NHS England. Currently, only cases undergoing screening for clinical trials are submitted to the program.

The difficulty surrounding thinking to test for CLN2 was highlighted by healthcare professionals, who noted that structural barriers for timely referral to specialists must also be overcome to ensure early diagnosis in early symptomatic patients, irrespective of any disease awareness (39). A patient will often have deteriorated in both their motor and language abilities by the time they are referred to a neurologist, the healthcare professional


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that typically makes the CLN2 diagnosis (39). Note, that once clinical suspicion is present all patients would be tested for CLN2 disease (42).

**CLN2 diagnosis progress since HST12**

During the July 2023 advisory board with patient advocates, participants agreed that obtaining a rapid diagnosis remains a challenge due to the non-specificity of symptoms and the lack of disease awareness among healthcare professionals (13). However, they were unanimous that there has been a slow and steady increase in awareness in the clinical community since 2019, likely due to the HST12 appraisal press coverage and as a result of additional treatment centres opening across the UK. They remarked that a shift in the awareness of CLN2 disease is taking place, with awareness generally spreading across the UK. One clinician based in Manchester – currently the centre treating the largest number of patients with CLN2 disease – noted that they are seeing a gradual shift towards improved ML scores at diagnosis (39).

In October 2023, Genomics England published a list of genes that will be included in the Newborn Genomes Programme's "Generation Study", which includes *CLN2/TPP1* (43). This study aims to evaluate the utility and feasibility of screening newborns for a larger number of childhood-onset rare genetic conditions in the NHS, using whole genome sequencing. The Generation Study is the first time that genome sequencing is being researched in a newborn screening context in the NHS on a national scale and may provide a step change in the way rare newborn diseases such as CLN2 disease are diagnosed and treated in England. Clinicians present at the July 2023 advisory board highlighted that national newborn screening for CLN2 disease is conceivable within the next five years, which would drastically improve the time to diagnosis, and a strong possibility for patients to present prior to first symptoms (equivalent to an ML score 6) at diagnosis, with one adviser agreeing that all newly diagnosed patients would present with a score of 6 (39).

Timely diagnosis will facilitate early initiation of disease-specific care, reduce the risk of inappropriate medications, enable families to make informed decisions as early as possible regarding the goals of care and family planning, and maximise the possibility of complete/long-term disease stabilisation with achievement of age-appropriate developmental milestones.

#### B.1.3.5.3. Management of CLN2 disease

Management of CLN2 disease involves symptomatic management, which are focused on the treatment of seizures (anticonvulsants), motor control loss (bracing or wheelchairs) and feeding/control of aspiration risk (gastrostomy tube or G-tube). Disease management also


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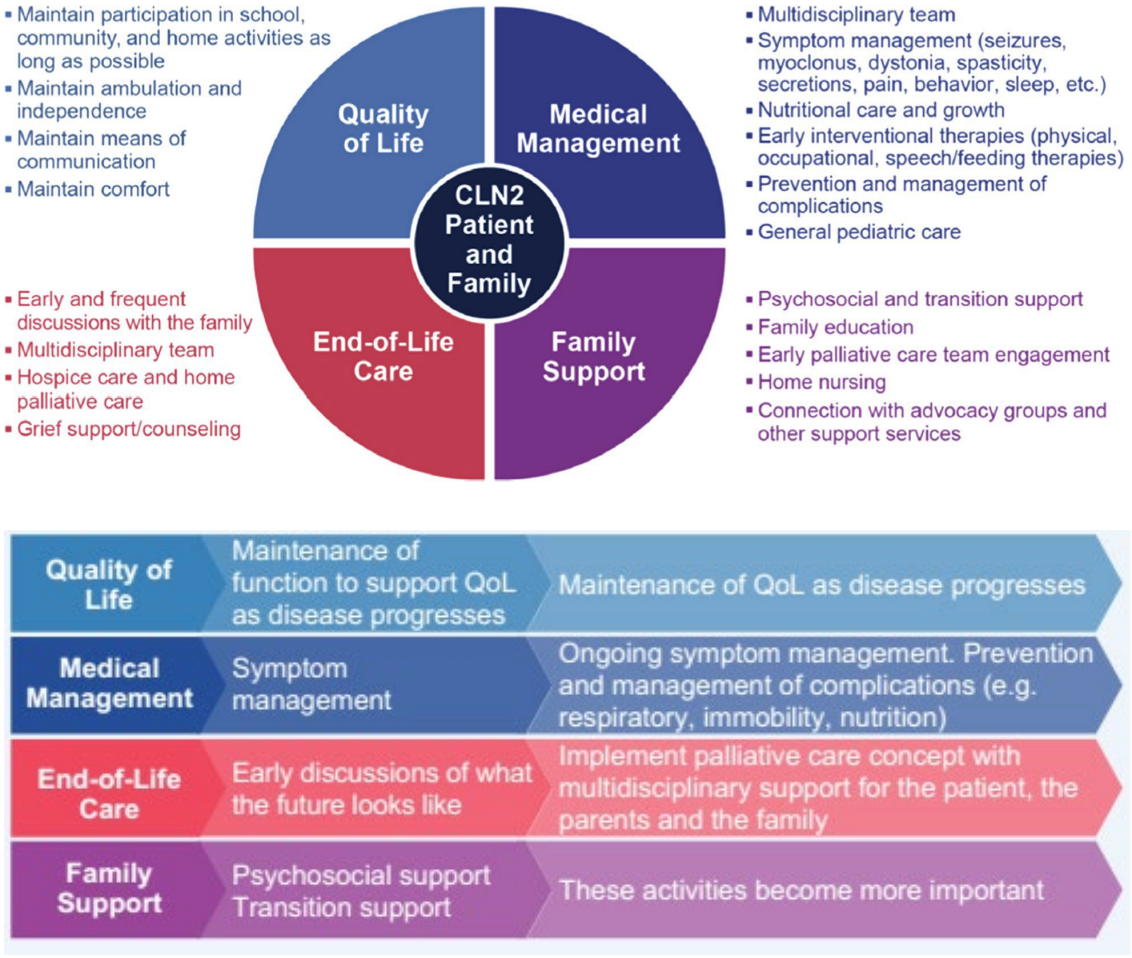
involves physical and speech therapies, medications to alleviate other disease symptoms (e.g. myoclonus, spasticity, dystonia, and pain), and palliative care.

Apart from cerliponase alfa, there are no treatments licensed or otherwise approved to treat CLN2 disease. Cerliponase alfa received a positive NICE recommendation within the context of a five year MAA in 2019 (HST12) (14), which will end in November 2024.

Prior to this agreement, and in the absence of treatments that targeted its underlying cause, a diagnosis of CLN2 disease was invariably fatal. Management was limited to symptomatic relief and supportive care. Management goals and strategies, defined by international clinical consensus, are guided by the principles of paediatric palliative care (15). These principles go well beyond medical management of the patient and extend to the support of the family beyond the life of the affected child. (15, 16) These can be considered under four main themes as laid out in Figure 3: (i) medical management of the child; (ii) QoL of the child and family; (iii) family support; and (iv) end of life care.


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**Figure 3: A palliative care framework for CLN2 disease management facilitates comprehensive care of patients and families**




Sources : Williams et al, 2017 (15); Mole et al, 2021 (16).
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; QoL, quality of life.

Due to the progressive nature of CLN2 disease, the goals of care evolve over time. In the early stages of disease, the overarching aim is to maintain function and involvement in mainstream activities for as long as possible. As the disease progresses, symptoms become more difficult to control, and patients are at greater risk of new complications, such as pressure sores due to immobility and aspiration from swallowing difficulties. The therapeutic goal thus evolves to maintaining HRQoL, despite the loss of function. In the later stages of disease, increasing levels of holistic, multidisciplinary support are required for the patient, caregivers and family, and discussion of end of life care involves planning and decision-making (15).

### B.1.3.5.4. Cerliponase alfa place in therapy

Cerliponase alfa is the only approved and licensed treatment that targets the underlying cause of CLN2 disease. Without cerliponase alfa availability, patients would be limited to symptomatic relief and supportive care, which includes both medication and other interventions to relieve symptoms and maintain function and HRQoL. CLN2 disease


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deprives the patient of a functional life from early childhood, which has a devastating impact on the QoL of parents, caregivers and families (13, 39). Ultimately, CLN2 disease is a devastating condition associated with poor QoL and a very short life expectancy, and before the MAA (resulting from HST12) there was a significant unmet need in terms of effective treatment options for patients with the disease.

Cerliponase alfa is a highly innovative, breakthrough technology which, since its positive recommendation and routine availability, has represented a step-change in the management of CLN2 disease in the UK. CLN2 disease requires direct cerliponase alfa administration to the central nervous system due to the blood brain barrier, which limits biodistribution of large molecules to the brain. The main innovation associated with cerliponase alfa is therefore the ICV route of delivery, as this is the first protein/ERT delivered via infusion directly to the brain.

Cerliponase alfa has shown significant clinical effectiveness and a manageable and consistent safety profile across various clinical trials. As demonstrated by the clinical trial data presented in Section B2, halting or slowing the decline of the CLN2 Clinical Rating Scale total score is clinically meaningful and is associated with improvement in the QoL of patients, parents and families (17, 18). Treatment with cerliponase alfa has allowed children with the disease to not only maintain function but to potentially gain new developmental milestones, and thus has had significant positive impact on the lives of patients, parents, caregivers, and families. In the longer term, these clinical benefits are expected to translate into reduced mortality and longer life expectancy for patients. Earlier diagnosis and treatment of children/babies with CLN2 disease is expected to lead to sustained clinical outcomes, as patients may stabilise and never show the classic manifestation of the disease, thus developing similar to other children and gaining developmental milestones.

Since the NICE appraisal of cerliponase alfa in 2019, there have been no significant changes to the pathway of care for CLN2 disease. There are currently no alternative treatments licensed or otherwise approved to treat CLN2 disease or its underlying cause. Prior to HST12, CLN2 disease management was limited to symptomatic relief and supportive care only, guided by the principles of paediatric palliative care. The value of cerliponase alfa (available under the MAA linked to HST12) to patients, families, society, and healthcare systems is characterised by its ability to stabilise or slow the progression of CLN2 disease, which has not been possible with other approaches. The full effect of benefits therefore goes far beyond the direct health benefits on patients with CLN2 disease.


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### B.1.4. Equality considerations

No issues relating to equity or equality that are relevant to this evaluation have been identified, other than to reiterate that CLN2 disease is an ultra-rare and life-limiting disease for which there are no current treatment options other than cerliponase alfa beyond the management of symptoms and palliative care.

Given the rapidly progressing nature of CLN2 disease, the accompanying loss of function across all domains, deteriorating HRQoL and poor survival prognosis, early diagnosis and treatment is vital for all patients, as is early and comprehensive access to multi-disciplinary supportive and palliative care. The expanded availability of treatment through the increase in number of specialist centres across England since HST12 have improved the equality of cerliponase alfa access.

Patients with CLN2 disease suffer from a range of symptoms, disabilities, and morbidity; treatment with cerliponase alfa has shown potential to stabilise disease in patients diagnosed at earliest symptoms, and delay disease progression in patients irrespective of starting ML score, thereby reducing and/or delaying the burden of morbidity and disability in these patients and reducing burden on their families.


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## B.2. Clinical effectiveness

**Since the original evidence submission HST12 (14), numerous new sources of clinical effectiveness evidence for cerliponase alfa in neuronal ceroid lipofuscinosis type 2 (CLN2) have become available. Studies 190-201/202, 190-203, and the MAA cohort now have final analyses. In addition, data from three long-term safety studies, and two supplementary studies (190-801 and DEM-CHILD-RX) have become available, all of which address the clinical uncertainties identified in HST12, in a relevant patient population, generalisable to the UK.**

**Long-term CLN2 disease stabilisation was achieved via cerliponase alfa treatment, as demonstrated via clinically meaningful and statistically significant slowing of disease progression across all relevant effectiveness studies, up to six years (5.56 years plus 24 weeks of follow-up):**

- The primary efficacy endpoint of time to unreversed motor language (ML) two-point decline or score of zero demonstrated a statistically significant difference in the cerliponase alfa treated group as compared with natural history (NH) controls (i.e. Study 190-901) across all relevant clinical effectiveness studies (11, 19, 44, 45)
- Attenuation of disease progression was also observed via the decreased rate of decline in ML score in cerliponase alfa treated participants vs NH controls across all relevant clinical effectiveness studies
- A dedicated survival analysis of treated vs untreated patients in 190-201/202 demonstrated that cerliponase alfa treatment significantly increased patient survival. The supportive analyses, showing a significant delay in time to reach an ML score of zero in the cerliponase alfa treated participants across all the presented clinical effectiveness studies, suggests that this increased survival is accompanied by significant preservation of patient function

**Improved CLN2 disease awareness, and newborn screening may pave the way for earlier diagnoses and improved cerliponase alfa treatment outcomes. The impact of initiating treatment in patients at earlier stages of disease progression was evidenced in Study 190-203, during which pre-symptomatic participants at baseline had a 5-fold reduction in the likelihood of consecutive motor, language, vision, and seizure function deterioration vs NH controls (19)**

- The 190-203 analysis observed no sustained ML score rate of decline in participants with baseline scores of 6 vs aggregate loss of function in matched NH, during the observed study period, demonstrating cerliponase alfa treatment causes a significant delay in time to disease manifestation
  - Addition of the vision and seizure domains to the ML scale, producing the MLVS full CLN2 Clinical Rating Scale, did not meaningfully change scores from baseline, indicative of a durable, multidomain treatment effect relative to NH controls (19)
- A subgroup analysis of participants who started cerliponase alfa prior to symptom onset, reported significantly delayed symptom onset and/or less severe and more easily managed CLN2 symptoms
- Whilst an initial loss of cortical grey matter followed by stabilisation was reported in participants ≥3 years, volumes were stable in treated participants <2 and <3 years, indicating that the earlier cerliponase alfa treatment is initiated, the more likely brain atrophy and CLN2 disease progression may be prevented
- Healthcare professionals from main expert centres in England are seeing improvements on the ML score starting distribution due to early diagnosis (39)


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**Cerliponase alfa treatment may reduce patient seizure and mobility deterioration, and can improve quality of life**

- Overall seizure activity in cerliponase alfa treated participants was stable, an effect not associated with changes in seizure medication (46). Additionally, cerliponase alfa treatment did not cause increased severity of seizures, as evidenced through a reduction in the need for doctor/hospital visits (46)
- Clinical experts validated that seizures have been easier to manage since the 2017 positive recommendation and the availability of cerliponase alfa treatment (39). They noted that seizures were both less frequent, and less severe in treated patients
- Studies examining patient movement disorders indicated that most cerliponase alfa treated patients did not experience increases in frequency or severity of involuntary movements (19, 46)
- During advisory boards with patient advocates and healthcare professionals, there was a consensus that patient, parent, and sibling QoL was significantly improved as a direct result of cerliponase alfa treatment (13, 39, 42)

**Additional, safety outcome evidence reinforces the previously reported positive benefit-risk profile of cerliponase alfa in CLN2 disease**

- Safety data from the completion of studies 190-201/202, 190-203, and the long-term safety data from studies 190-501, 190-502, and 190-504 have all validated that the administration of cerliponase alfa is generally well tolerated (19, 44, 47-49).

## B.2.1. Identification and selection of evidence

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of cerliponase alfa and relevant comparators for the treatment of patients with CLN2. In total, the SLR identified 70 publications reporting on 41 studies. See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

Of the included studies, 12 publications (including one HTA report) reporting on three BioMarin studies (190-201, 190-202, and 190-203) were identified that evaluated cerliponase alfa for CLN2. A summary of identified study references is provided in Table 7.

**Table 7: Identified clinical effectiveness evidence**

| Study name, trial number, phase | Intervention | Comparator | Author, year/source |
|---|---|---|---|
| Study 190-201<br>NCT01907087<br>Single-arm open label study | Cerliponase alfa | N/A | Schulz 2016 (50); Gissen 2017 (51); Specchio 2017 (52); Schulz 2018 (53); Schulz 2020b (54); SMC 2020 (55) |
| Study 190-202<br>NCT02485899<br>Single-arm open label extension study | Cerliponase alfa | N/A | Schulz 2016 (50); Schulz 2017 (56); Schulz 2018 (53); SMC 2020 (55); Schulz 2024 (57) |


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| Study name, trial number, phase | Intervention | Comparator | Author, year/source |
|---|---|---|---|
| Study 190-203<br>NCT02678689†<br>Single-arm open label extension study | Cerliponase alfa | N/A | Schulz 2020 (58);<br>Schulz 2021 (59);<br>*Schulz 2023a (21)†;*<br>*Schulz 2023b (20)†* |

†Data from Study 190-203 were presented at a conference and were not captured in the SLR update search.
Abbreviations: N/A, not applicable; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

## B.2.2. List of relevant clinical effectiveness evidence

In HST12, the main clinical evidence was derived from three studies (190-201, 190-202, and 190-901):

- Study 190-201 was a single-arm open-label study including 24 patients aged three years to 16 years with late-infantile CLN2 treated with cerliponase alfa. Patients were enrolled from the US, Germany, Italy, and the UK. Follow-up was 48 weeks.
- After the completion of 190-201, patients were enrolled in an extension study (190-202) for long-term follow-up. All patients who completed 190-201 transitioned to 190-202, in which data was reported for an additional 28 weeks
- Study 190-901 was a natural history (NH) study that retrospectively evaluated disease progression in patients with untreated CLN2 (included in the DEMCHILD database) (Section B.2.3.4). To provide comparative data for the efficacy outcomes in 190-201/202, data were retrospectively matched to the NH participants using a 1:1 matching algorithm.

Since the original NICE HST submission in 2017 (14) the following data have become available and are presented in this submission:

- New data were reported for **Study 190-201/202**, which was completed in December 2020 with an additional 49 months of follow-up since the HST12 submission. With a total treatment duration of 289 weeks (49 weeks in study 190-201 + 240 weeks in study 190-202), the long-term study 190-201/202 thus covers a period of 5.56 years plus 24 weeks of follow-up, and is the longest follow-up for patients with CLN2 treated with cerliponase alfa

- Data were reported for **Study 190-203**, completed in April 2022 with 169 weeks of follow-up. This study was a post-marketing commitment that primarily enrolled children <3 years of age and required enrolment of at least five participants <2 years of age (19). As 190-201/202 enrolled patients >3 years, this study aimed to provide additional long-term clinical evidence for cerliponase alfa for CLN2 in a population more generalisable to the UK


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- Cerliponase alfa received a positive recommendation within the context of a managed access arrangement (**MAA**). The purpose of this agreement was to describe the uncertainties identified by NICE's technology appraisal committee, patient eligibility criteria, and arrangements intended to capture the data that may address these uncertainties. The MAA cohort was established to collect real-world evidence (RWE) to support this re-evaluation by NICE

- New long-term safety data have been reported in **Studies 190-501**, **190-502**, and **190-504**.

Additionally, evidence from the following studies has become available and is provided as supplemental clinical effectiveness evidence to this submission:

- Data were reported for **DEM-CHILD-RX**, a RWE registry study that provided a retrospective analysis of clinical data from patients enrolled in the DEM-CHILD database; an ongoing, multicentre, multinational clinical database based in Hamburg, Germany. The database collects clinical, laboratory, and imaging data as well as information on the development of patients with NCL (including CLN2 disease). DEM-CHILD-RX represents an extension of the original dataset from Hamburg, which also includes data on the NH of the disease. This dataset contains patients treated with cerliponase alfa who have not previously participated in clinical trials

- Interim data (Wave 1) were reported for **Study 190-801**, a long-term ongoing retrospective analysis of the DEM-CHILD registry aimed at evaluating long-term effectiveness of cerliponase alfa in patients with CLN2, in addition to changes in disease progression and symptomatology of CLN2 disease. Specifically, Wave 1 objectives included capturing changes in seizures, movement disorders/ambulation status, and patient reported outcome (PRO) measures.

An overview of the clinical evidence included in this submission is provided in Table 8.


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**Table 8: Summary of clinical effectiveness evidence: efficacy and safety outcomes**

| Study | HST12 (DCO) | Review of HST12 (DCO) | Weeks of follow-up | Submission section |
|---|---|---|---|---|
| 190-901 | ✓ 30th June 2016 | ✓ 30th June 2016 | NR | Section B2 and Appendix M |
| 190-201/202 | ✓ 3rd June 2016 | ✓ 10th December 2020 | 289 | Section B2, Appendix O and Appendix F |
| 190-203 | × | ✓ 20th April 2022 | 169 | Section B2, Appendix O and Appendix F |
| MAA cohort | × | ✓ 1st September 2023 | 209 | Section B2 |
| 190-501 | × | ✓ 9th March 2023 | 104† | Section B2 and Appendix F |
| 190-502 | × | ✓ 7th September 2017 | 31 | Section B2 and Appendix F |
| 190-504 | × | ✓ 26th April 2023 | 151† | Section B2 and Appendix F |
| DEM-CHILD-RX | × | ✓ 31st December 2020 | 26‡ | Appendix P |
| 190-801 | × | ✓ December 2022 | N/A‡ | Appendix Q |

†Median cerliponase alfa exposure time;‡ Participant follow-up was started at different timepoints, duration of follow-up therefore varied for patients. Minimum follow-up was 6 months (i.e. 2 assessments).
Abbreviations: DCO, data cut-off; HST, highly specialised technology; MAA, managed access arrangement.

Study characteristics for the relevant clinical effectiveness and safety evidence can be found in Table 9 and Table 10.


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**Table 9: Clinical effectiveness evidence**

| Study | 190-201[†] | 190-202 | 190-203 (PAES) | MAA data | NH control |
|---|---|---|---|---|---|
| Study design | Interventional study. Open-label, Phase 1/2 | Interventional study. Open label, Phase 2. Designed as an extension to Study 190-201 | Interventional study. Open-label, Phase 2 | Clinical data collection agreement | Observational NH study – retrospective DEM-CHILD database review |
| Patient population | Patients with confirmed CLN2 disease treated with the study intervention and compared with a NH control group | | | | Untreated (NH) patients with CLN2 disease included in the database |
| No of UK patients | 4 | 4 | 1 | 35 | None |
| Intervention(s) | Cerliponase alfa | | | | N/A |
| Comparator(s) | NH cohort (Study 190-901 supplement) | | | | N/A |
| Study supports application for marketing authorisation | Yes | Yes | No | No | Yes |
| Study used in the economic model | Yes | Yes | Yes | Yes | Yes |
| Reported outcomes specified in the decision problem[‡] | • **Symptoms of CLN2 including visual function, seizures, myoclonus, dystonia**<br>• **Disease progression**<br>  ○ **CLN2 Clinical Rating Scale (reported as 4-domain scale and combined score of the motor and language domains [ML score])**<br>• **Concomitant medication**<br>• **Mortality**<br>• **Adverse effects of treatment (including immune response and effects and complications related to treatment administration)**<br>• HRQoL informed by QoL measures including PedsQL, **EQ-5D**, and CLN2-QL<br>• **Compliance/adherence to treatment** | | | • **Symptoms of CLN2 including visual function, seizures, myoclonus, dystonia**<br>• **Disease progression**<br>  ○ **CLN2 Clinical Rating Scale (reported as 4-domain scale and combined score of the motor and language domains [ML score])**<br>  ○ Weill Cornell LINCL Scale<br>• Neurological development measures, including Bayley Scales of Infant Development III, WPPSI-IV, Vineland Adaptive Behaviour Scale, and WISC-V<br>• **Mortality** | N/A |


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| Study | 190-201† | 190-202 | 190-203 (PAES) | MAA data | NH control |
|---|---|---|---|---|---|
| | | | | • HRQoL informed by QoL measures including PedsQL, **EQ-5D**, and CLN2-QL<br>• **Compliance/ adherence to treatment** | |
| All other reported outcomes | Safety, tolerability, pharmacokinetic, and efficacy | Safety, tolerability, and efficacy | | Efficacy | NH patient characteristics. Disease-specific clinical scales, disease progression rate and variability after onset of clinical symptom¶ |
| Key publications | EUCTR2012-005430-11-GB (60); Cherukuri, 2017 (61) | Schulz 2024 (57); Schulz 2016a (62); EUCTR2014-003480-37-GB (63); NCT02485899 (64) | NCT02678689 (65); *Schulz 2023a (21)††; Schulz 2023b (20)††* | NICE, 2019 (66) | MHRA (24) |
| Secondary sources | BioMarin 190-201/202 CSR (17); NCT01907087 (67)<br>Schulz 2016a (62)<br>Schulz 2016b (50)<br>Schulz 2016c (68)<br>Schulz 2016d (69) | BioMarin 190-201/202 CSR (17) | BioMarin 190-203 CSR, 2023 (19) | BioMarin MAA database, 2023 (11) | BioMarin 901 CSR, 2016 (45) |

†The study included a dose escalation phase in a subset of patients to establish a maximally tolerated dose; ‡Outcomes incorporated in model are shown in bold; ¶Including onset and variability of the first clinical symptoms (disease onset). Clinical symptom(s). Distribution of age at diagnosis. Relationship of genotype to clinical course. Relationship of MRI assessment to clinical severity and patient age. Patient age and disease severity of two independent patient cohorts; ††Data from Study 190-203 were presented at a conference and were not captured in the SLR update search

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ECG, electrocardiogram; EEG, electroencephalogram; HRQoL, health-related quality of life; MAA, managed access agreement; MRI, magnetic resonance imaging; N/A, not applicable; NH, natural history; NR, not reported; OCT, optical coherence tomography; PAES, post-authorisation efficacy study; PedsQL, Pediatric Quality of Life Inventory QoL, quality of life; UK, United Kingdom ; WISC-V, Wechsler Intelligence Scale for Children fifth edition; WPPSI-IV, echsler PreSchool and Primary Scale of Intelligence.


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**Table 10: Additional relevant clinical safety and tolerability evidence**

| Study | 190-501 | 190-502 | 190-504 (PASS) |
|---|---|---|---|
| Study 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 |
| Patient 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 |
| No of UK patients | 0; US patients only | 6 | 7 |
| Intervention(s) | Cerliponase alfa | | |
| Comparator(s) | N/A | | |
| Indicate if study supports application for marketing authorisation | No | | |
| Indicate if study used in the economic model | No | | Yes |
| Rationale if study not used in model | Additional information on the safety and tolerability of cerliponase alfa administration in patients with CLN2 disease was not used to inform the model | | |
| Reported outcomes specified in the decision problem | Adverse effects of treatment (including immune response and effects and complications related to treatment administration) | | |
| All other reported outcomes | Long-term safety and tolerability of cerliponase alfa | | |
| Key publications | N/A | NCT02963350 (70) | N/A |
| Secondary sources | 190-501 annual report no 6 (47) | 190-502 CSR (48) | 190-504 annual report no.6 (49) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; N/A, not applicable; PASS, post-authorisation safety study; UK, United Kingdom; US, United States.


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### B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

An overview of the relevant clinical effectiveness evidence for cerliponase alfa is provided in Sections B.2.3.1 to B.2.3.3, with the NH control described in Section B.2.3.4. Table 11 presents a summary of the methodology of the relevant clinical effectiveness evidence. An overview of cerliponase alfa long-term safety studies is presented in Section B.2.3.5, and Appendix F. Supportive supplementary studies DEM-CHILD-RX and Study 190-801 are described in Appendix P and Appendix Q, respectively.


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**Table 11: Summary of methodology of the relevant clinical effectiveness evidence**

| Study name | Study 190-201/202 | Study 190-203 | MAA | NH (Study 190-901) |
|---|---|---|---|---|
| **Objective** | To evaluate the efficacy and safety of doses up to 300 mg/every other week cerliponase alfa in patients with CLN2. The dose and regimen for this Study 190-202 are based on the results of the Study 190-201. The rationale for this Phase 2 extension study is to provide patients who completed the Study 190-201 with the option to continue receiving cerliponase alfa treatment. Study 190-202 is an open label extension protocol to assess long-term safety and efficacy | • To evaluate the safety, tolerability, and efficacy of cerliponase alfa ICV administration at an age-appropriate dose every other week for a period of 96 weeks, in patients with CLN2<br>• To assess disease progression in CLN2 patients treated with cerliponase alfa compared with NH, data from untreated historical controls (Study 190-901) | • To address key uncertainties as identified in the Final Evaluation Document issued by NICE (14)<br>• To understand changes in clinical and PROs over time for patients with CLN2 disease treated with cerliponase alfa in England, for the purposes of 6-monthly assessments by the MAOG (as defined in the MAA)<br>• To populate and update the cost-effectiveness (CEM) and budget impact (BIM) models originally submitted to NICE as part of HST12 with relevant parameters and analyses of the MAA data, where feasible | To analyse data from NH patients with CLN2 disease to provide a historical comparator for Study 190-201/202, by evaluating the disease progression and variability after onset of clinical symptoms using disease-specific Clinical Rating Scales |
| **Location(s)** | US, Germany, Italy, UK | US, Germany, UK, Italy | UK | Germany, Italy |
| **Duration of study** | Up to 240 weeks | Up to 96 weeks | Approximately 5 years | NR |
| **Sample size** | 24; participants were enrolled in Study 190-201 and comprise the safety population. The efficacy analysis consisted of 23 ITT participants | 14 | 35¶ | 42 (of which 17 were used in the 1:1 matched analysis of Study 190-201/202; 29 were used in the 3:1 matched analysis of Study 190-203; 26 were used in the 1:1 matched analysis of the MAA FAS; 17 were used in the 1:1 matched analysis of the MAA new starter cohort) |
| **Inclusion criteria** | • Patients must have completed 48 weeks in Study 190-201<br>• Patents willing and able to provide written, signed informed consent. Or, in the case of patients under the age of 18 (or other age as defined by regional law or regulation), provide | • Diagnosis of CLN2 disease as determined by TPP1 enzyme activity (dried blood spot) in the fibroblasts and leukocytes available at screening.<br>• Quantitative clinical assessment of the Hamburg ML aggregate score 3–6 at | Patients in England who transfer from the clinical trial or expanded access program (ex-trial cohort) are eligible if they meet the following criteria:<br>• Patients or their guardians sign up to the 'Managed Access Patient Agreement | Applied to the patients in the DEM-CHILD database, matching key eligibility criteria for Study 190-201:<br>• At least 2 evaluations of CLN2 Clinical Rating Scale at age of ≥36 months |


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| Study name | Study 190-201/202 | Study 190-203 | MAA | NH (Study 190-901) |
|---|---|---|---|---|
| | written assent (if required) and have written informed consent, signed by a legally authorised representative, after the nature of the study has been explained, and prior to performance of research-related procedures<br>• Males and females who are of reproductive age should practice true abstinence, defined as no sexual activity, during the study and for 6 months after the study has been completed (or withdrawal from the study). If sexually active and not practicing true abstinence, males and females of reproductive age must use a highly effective method of contraception while participating in the study<br>• If female, of childbearing potential, must have a negative pregnancy test at the screening visit and be willing to have additional pregnancy tests done during the study | screening on CLN2 disease ML scale, as defined in the Ratings Assessment Guideline<br>• Age <18 years of age at the time of informed consent<br>• Written informed consent from parent or legal guardian and assent form subject, if appropriate<br>• Ability to comply with protocol required assessments (ICV implantation, drug administration, laboratory sample collection, EEG, ECG, MRI, etc.)<br>• Males and females who are of reproductive age should practice true abstinence, defined as no sexual activity, during the study and for 6 months after the study has been completed (or withdrawal from the study). If sexually active and not practicing true abstinence, males and females of reproductive age must use a highly effective method of contraception while participating in the study | Patients in England who start treatment under the MAA (i.e. not transfer from the clinical trial and expanded access program) (MAA new starter patient cohort) are eligible if they meet the following criteria:<br>• Must have a confirmed diagnosis of CLN2 on the basis of clinical information and enzymatic activity test<br>• Not diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit, e.g. cancer or multiple sclerosis<br>• The patient has a CLN2 rating scale ML Score of >2<br>• Patients or their guardians sign up to the 'Managed Access Patient Agreement' | • At least 1 score of CLN2 Clinical Rating Scale ≥3<br>• At least 2 scores of CLN2 Clinical Rating Scale between 1 and 5<br>• At least 1 rating of CLN2 Clinical Rating Scale ≥6 months after first rating |
| **Exclusion criteria†** | • Patients who have had a loss of 3 or more points in the combined motor and language components of the CLN2 rating scale between baseline of Study 190-201 and the study completion visit in Study 190- | • Presence of another inherited neurological disease, e.g. other forms of CLN or seizures unrelated to CLN2 disease (patients with febrile seizures may be eligible) | All patients will cease therapy with cerliponase alfa if any of the following apply:<br>• The patient is non-compliant with assessments for continued therapy (non-compliance is defined as <2 attendances for assessment in any | NR |


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| Study name | Study 190-201/202 | Study 190-203 | MAA | NH (Study 190-901) |
|---|---|---|---|---|
| | 201 and would not benefit from enrolling in the study in the investigator's discretion<br>• Patients with a score of 0 points on the combined motor and language components of the CLN2 rating scale<br>• Pregnant or breastfeeding patients, at baseline, or planning to become pregnant (self or partner) at any time during the study<br>• Patients who have use any investigational agent prior to completion of all scheduled study assessments<br>• Patients with a concurrent disease or condition that would interfere with study participation, or pose a safety risk, as determined by the investigator<br>• Patient with any condition that, in the view of the investigator, places the patient at high risk of poor treatment compliance or of not completing the study | • Presence of another neurological illness that may have caused cognitive decline (e.g. trauma, meningitis, haemorrhage) or interference with disease rating (autism) before screening<br>• Presence of percutaneous feeding tube placement prior to enrolment<br>• Has received stem cell, gene therapy, or ERT<br>• Presence of contraindications for neurosurgery (e.g. congenital heart disease, severe respiratory impairment, or clotting abnormalities)<br>• Presence of contraindications for MRI scans (e.g. cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain)<br>• Episode of generalised motor status epilepticus within 4 weeks before the first dose visit<br>• Severe infection (e.g. pneumonia, pyelonephritis, or meningitis) within 4 weeks before the first dose visit (enrolment may be postponed)<br>• Presence of ventricular abnormality (hydrocephalus, malformation)<br>• Presence of ventricular shunt | 14-month period excluding medical reasons for missed dosages); or<br>• The patient is unable to tolerate infusions due to infusion related SAEs or any other clinical concerns that cannot be resolved and have been discussed with NHS England or the MAOG; or<br>• 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<br>Patients aged 3 years and over, who have been receiving treatment for <18 months will be stopped if both of the following non-response criteria are met:<br>• A loss >2 points (i.e. 3 or more points) on the CLN2 Rating Scale ML score from baseline within 18 months of the first infusion and a total CLN2 rating scale score of <2:<br>• 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)<br>And<br>During the first 18 months of treatment, a reduction in proxy reported patient QoL of:<br>• ≥15 points on the PedsQL total score (which is 3 times the minimal clinically important difference); and<br>• 0.23 drop in utility as measured by the EQ-5D-5L and<br>• Decline in CLN2 QoL assessment of ≥15 points. | |


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| Study name | Study 190-201/202 | Study 190-203 | MAA | NH (Study 190-901) |
|---|---|---|---|---|
| | | • Has known hypersensitivity to any of the components of cerliponase alfa<br>• Has received any investigational mediation within 30 days before the first infusion of study drug or is scheduled to receive any investigational drug other than cerliponase alfa during the course of the study<br>• Has a medical condition or extenuating circumstance that, in the opinion of the investigator, might compromise the subject's ability to comply with the protocol required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability<br>• Pregnancy any time during the study; a female subject judged by the investigator to be of childbearing potential will be tested for pregnancy | 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.<br>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 >18 months. These patients should be stopped from receiving further treatment due to non-response, if they meet the following criteria:<br>• A loss of >1 point (i.e. 2 or more points) on the CLN2 Rating Scale ML score, in the previous 12 months and a total CLN2 rating scale score of <2;<br>• 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)<br>Or<br>• Progression to an unreversed score of 0 on the CLN2 Rating Scales ML score<br>• 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.<br>And<br>• A reduction in proxy reported patient QoL in the previous 12-month treatment window of | |


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| Study name | Study 190-201/202 | Study 190-203 | MAA | NH (Study 190-901) |
|---|---|---|---|---|
| | | | • ≥15 points on the PedsQL total score (which is 3 times the minimal clinically important difference); and<br>• 0.25 drop in utility as measured by the EQ-5D-5L and<br>• Decline in CLN2 QoL assessment of ≥15 points<br>If a patient is ill prior to an assessment, then the patient needs to be reassessed within 12 weeks and subsequent measures need to be considered from this point | |
| **How were participants followed-up** | Following either the study completion visit (Week 239) or the early termination visit, arrangements were to be made for removal of the ICV access device. If the subject intended to continue to receive cerliponase alfa following participation in this study (e.g. via commercial product, or another clinical study), then the device was not removed. Device removal was to occur no more than 4 weeks after the last administration of study drug.<br>A device removal safety follow-up visit was to be performed within 4 weeks (±3 days) from removal of the ICV access device. | 190-203 participants were given the opportunity to enrol in a post-marketing observational safety study. These studies are evaluating the long-term safety of cerliponase alfa in patients with CLN2 disease. Participants have the option to enrol at sites in the US (**Study 190-501**) or the EU (**Study 190-504**). Clinical and safety assessment data will be collected as indicated according to SoC for approximately 10 years. | MAA participants will continue to receive treatment under the MAA until November 2024. | NR |
| **Statistical methods** | Section B.2.4.1 | Section B.2.4.2 | Section B.2.4.3 | Section B.2.4.4 |


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| Study name | Study 190-201/202 | Study 190-203 | MAA | NH (Study 190-901) |
|---|---|---|---|---|
| **Primary outcomes‡** | **CLN2 Clinical Rating Scale – ML subscale.** A number of analyses were carried out on the primary endpoint, including;<br>• Responder analysis: percentage of patients with a less than 2-point decline per 48 weeks<br>• Survival analysis: time taken to achieve a 2-point scale score change<br>• Slope analysis: rate of decline in score per 48 weeks<br>• Time to unreversed ML score of zero: represents most severe/progressed state of the disease as captured by the ML scale. | | | |
| | To evaluate the long-term safety of cerliponase alfa | – | – | |
| **Key secondary outcomes‡** | CLN2 clinical rating scale total score and individual domains: motor, language, vision, seizure | | | |
| | **Brain atrophy**: Measurement after 48 weeks of treatment. MRI was performed at baseline for the 300 mg stable dose period and at weeks 9, 25 and 49 in Study 190-201, at 24-week intervals and at study completion in Study 190-202 and Study 190-203. Study 190-203: 6/13 participants at Week 145 missed their MRI assessment; most MRIs were missed due to COVID-19 related hospital mandates (19) | | | |
| | – | Time to disease manifestation for asymptomatic participants | **Neurodevelopmental Assessment tools:** Bayley Scales of Infant Development III; Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV); Vineland Adaptive Behaviour Scale | – |
| **Exploratory/ other outcomes‡** | A number of variables were evaluated to explore the impact of treatment on age-appropriate developmental milestones and QoL:<br>• PedsQL™ Measurement Model for Pediatric Quality of life Inventory: PedsQL™ Generic Core and Parent Family Impact Module<br>• CLN2 QL Instrument<br>• EQ-5D-5Lt | | | |
| | Denver II Developmental Screening Test, VA, OCT, EEG | | OCT, EEG | |
| | – | mUBDRS involuntary movement inventory and seizure inventory: | | |

†Stopping criteria for the MAA cohort; ‡For more information/details on outcomes measured refer to Appendix M; ¶As of the September 2023 data cut-off.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ECG, electrocardiogram; EEG, electroencephalogram; ERT, enzyme replacement therapy; EQ-5D-5L, EuroQol-5 Dimension-5 Level questionnaire; FAS, full analysis set; ICV, intracerebroventicular infusion; ITT, intent-to-treat; MAA, managed access agreement; MAOG, Managed Access Oversight Group; ML, motor language; MRI, magnetic resonance imaging; mUBDRS, modified unified Batten disease rating scale; NH, natural history; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; OCT, optical coherence tomography; PedsQL, Pediatric Quality of Life Inventory; PRO, patient reported outcomes; QoL, quality of life; SAE, severe adverse event; SoC, standard of care; TPP1, tripeptidyl peptidase 1; UK, United Kingdom; US, United States; VA, visual acuity.


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### B.2.3.1. Study 190-201/202

Study 190-201 was the first open-label Phase 1/2 interventional study to assess the application of cerliponase alfa in children with confirmed CLN2 disease. The study aimed to evaluate safety, efficacy, and pharmacokinetics of the therapy (Appendix O). After its completion in November 2015, participants were enrolled in an extension study (Study 190-202) (57, 62). The Phase 2 extension Study 190-202 was designed as a long-term follow-up to Study 190-201, allowing patients from Study 190-201 to continue treatment with cerliponase alfa. Study 190-202 assessed long-term safety and efficacy and was completed December 2020, with an additional 49 months of follow-up since the 28 weeks of data presented in HST12 (44, 57, 62).

All participants who completed 48 weeks of cerliponase alfa treatment in 190-201 were eligible to enrol in 190-202. The screening period for 190-202 started simultaneously with the Week 47 visit in 190-201. Baseline values for 190-202 were recorded on the day of the first infusion (Week 1, Day 1) of 190-202, for all participants on active treatment. The first dose of cerliponase alfa in 190-202 (Week 1/ Day 1) was given following the Week 49 study assessments in 190-201. This study was open label, with all participants continuing treatment with 300 mg cerliponase alfa every 14 days for up to Week 239 (last 190-202 dosing visit).

Safety and efficacy data from 190-201 were combined with data from 190-202 to characterise the safety and efficacy of long-term treatment with cerliponase alfa. Efficacy analyses of CLN2 rating scales included analyses on the full patient population and a comparison with a NH database (190-901 [Section B.2.3.4]), based on 1:1 matching.

#### B.2.3.1.1. Baseline characteristics – Study 190-201/202 and NH matched patients

The baseline characteristics for the matched populations for the 48-week analysis are shown in Table 12.

**Table 12: Baseline characteristics for NH and 190-201/202 (1:1 matched patients)**

| | NH (n=17) | 190-201/202† (n=17‡) |
|---|---|---|
| Age at enrolment in 190-201 (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%) |


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| | NH (n=17) | 190-201/202† (n=17‡) |
|---|---|---|
| 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%) |

Source: Schulz et al, 2024 (57).
†ITT population; ‡Of the six participants who did not meet matching criteria, three had an unreversed 2-point decline or score of 0. This is consistent with 12/23 participants with a similar decline in the full set.
Abbreviation: CLN2, neuronal ceroid lipofuscinosis type 2; SD, standard deviation.

The most common drug classes received were benzodiazepine derivatives (100%), anilids and other general anaesthetics (96% each), fatty acid derivatives and glucocorticoids (88% each), and other antiepileptics, piperazine derivatives, propionic acid derivatives, and solutions affecting the electrolyte balance (83% each) (44).

The mean (SD) percent for dosing compliance, defined as actual dose/total planned dose × 100, was 98.5% (2.25) over the entire dosing period and the 300 mg dosing period (44).

### B.2.3.2. Study 190-203

Study 190-203 was a Phase 2, open-label, single arm, multicentre study in paediatric patients <18 years of age with CLN2 disease. Completed in April 2022, the study aimed to evaluate the safety, tolerability, and efficacy of cerliponase alfa in CLN2 patients compared with untreated NH controls. This study was a post-marketing commitment to both the European Medicines Agency (EMA) and the US Food and Drug Administrated (FDA) (25), that primarily enrolled children <3 years of age and required enrolment of at least five participants <2 years of age (19).

#### B.2.3.2.1. Baseline characteristics – Study 190-203 ITT and NH matched patients

Table 13 provides a comparison of the baseline characteristics for the matched NH and Study 190-203 populations.

**Table 13: Baseline characteristics for NH and 190-203 (3:1 matched patients)**

| | NH (N=29) | 190-203 (N=12§) |
|---|---|---|
| Age at baseline, years | | |
| Mean (SD) | 2.7 (1.09) | 2.7 (1.12) |
| Median (min, max) | 2.5 (1.1, 4.5) | 2.5 (1.1, 4.5) |
| Sex, n (%)† | | |
| Female | 15.3 (52.8%) | 8 (66.7%) |
| Male | 13.7 (47.2%) | 4 (33.3%) |


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| | NH (N=29) | 190-203 (N=12§) |
|---|---|---|
| Genome n (%)†,‡ | | |
| None | 2.4 (8.3%) | 1 (8.3%) |
| One key mutation | 9.7 (33.3%) | 4 (33.3%) |
| Two key mutations | 16.9 (58.3%) | 7 (58.3%) |
| CLN2 motor score | | |
| Mean (SD) | 2.6 (0.54) | 2.4 (0.79) |
| Median (min, max) | 3.0 (1.0, 3.0) | 3.0 (1.0, 3.0) |
| CLN2 language score | | |
| Mean (SD) | 2.4 (0.93) | 2.6 (0.67) |
| Median (min, max) | 3.0 (0.0, 3.0) | 3.0 (1.0, 3.0) |
| 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) |
| CLN2 MLVS score | | |
| n | 28 | 12 |
| Mean (SD) | 10.2 (2.73) | 10.9 (1.56) |
| Median (min, max) | 12.0 (4.0, 12.0) | 12.0 (8.0, 12.0) |
| 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) |
| Age of first seizure, years | | |
| n | 11 | 5 |
| Mean (SD) | 3.1 (0.31) | 3.0 (0.50) |
| Median (min, max) | 3.1 (2.5, 3.7) | 3.2 (2.5, 3.6) |

Source: Study 190-203 CSR, 2023 (19)
†Percentages were calculated using the total number of participants in ITT Population and in matched participants as the denominators separately. The 190-901 (NH) participants were weighted according to number of matches: weights for 3, 2, and 1 study 190-901 participant matched to a given study 190-203 participant were1/3,1/2, and 1 times N901/N203 respectively. N901 was the number of 190-901 participants matched to 190-203 participants (i.e. 29), and N203 was the number of 190-203 participants who had matches (i.e. 12). The 190-203 participants who had matches were assigned the weight of 1; ‡The common alleles were c.509-1G and c.622C>T; ¶Defined as age at first symptom; §The two oldest participants in the 190-203 ITT population (N=14) were excluded from the 190-203 ITT analysis with matching (N=12) who did not match with any 190-901 participants on the matching criteria. One participant (baseline ML=4, baseline age =4.8 years, genome =one key mutation) maintained the baseline score of ML=4 throughout the study follow-up, including the 24-week safety follow-up. Matching was exact on ML score and genetics and required age within 3 months...
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; MLVS, motor-language-vision-seizure; SD, standard deviation.

During 190-203, all participants received general anaesthetics (propofol in 92.9% of participants) and piperazine derivatives (cetirizine hydrochloride in 92.9% of participants). Thirteen participants each (92.9%) received glucocorticoids and propionic acid derivatives (19).

The mean (SD) percent for dosing compliance, was 97.3% (6.87) over the entire dosing period and 97.4% (6.62) over the 300 mg dosing period.


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### B.2.3.3. Managed access agreement (MAA)

In England, access to cerliponase alfa was granted to all patients on a conditional basis through the MAA for five years (until November 2024) (14). Key uncertainties highlighted by the committee in HST12 were long-term disease stabilisation, and improvements in motor and language (ML) score starting distribution. Further areas of uncertainty were: CLN2 Clinical Rating Scale scores over time; the frequency and severity of tonic-clonic seizures; myoclonus and dystonia control; visual acuity (VA); extra-neurological symptoms; cause of mortality; and measures of QoL.

The data collection agreement (DCA) was a collaboration between NHS England, NICE, treating clinicians, Rare Disease Research Partners (RD-RP) (legally represented as MPS Commercial UK), and BioMarin. For patients to maintain access to therapy, data were collected and reviewed by a clinical panel led by NHS England and treating clinicians on a biannual basis. Parents or a legal guardian of the patient were required to sign the Managed Access Patient Agreement before the start of cerliponase alfa treatment in England. The MAA therefore represents all patients with CLN2 eligible for cerliponase alfa treatment in England. Enrolment date was defined as the date of Managed Access Patient Agreement signature.

Under the MAA terms, a data collection process for all patients who start or receive treatment with cerliponase alfa during the term of the MAA was defined (Table 11). Patients who stopped treatment during the MAA period ceased to have data gathered under the MAA (71).

#### B.2.3.3.1. Baseline characteristics – MAA and NH matched patients

Table 14 provides a comparison of the baseline characteristics for the matched NH and MAA evaluable populations.

**Table 14: 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%) |


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| | 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†) |
| Baseline ML score | | | | |
| Mean (SD) | 4 (1.26) | 4 (1.26) | 4.12 (1.11) | 4.12 (1.11) |
| Median (min, max) | 4 (1, 6) | 4 (1, 6) | 4 (2, 6) | 4 (2, 6) |
| Categorical 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 |
| Median (min, max) | 36 (18, 48) | 34.5 (31, 36) | 36 (30, 48) | NR |

Source: BioMarin MAA database, 2023 (11).
†Defined as age at first symptom.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; MAA, managed access agreement; ML, motor language; NH, natural history; SD, standard deviation.

The mean (SD) percent for dosing compliance was ~97% over the entire dosing period. The number of missed infusions per cohort and assessment are reported in Appendix R.

### B.2.3.4. Natural history controls (Study 190-901)

Study 190-901 was designed and used as a NH study during HST12, in order to support the assessment of efficacy outcomes in Study 190-201/202. It will also serve as a comparison of the new clinical effectiveness data for cerliponase alfa in CLN2 since HST12 (25, 45).

#### B.2.3.4.1. Purpose and design of natural history analysis

The purpose of the 190-901 NH analysis was to enhance understanding of the disease course in untreated patients and to provide the most robust estimate of the rate of decline of scores on the CLN2 Clinical Rating Scale to support the assessments of efficacy in Study 190-201. The analytical methodology was therefore defined to align with the planned analyses for the Study 190-201 and was refined in discussion with regulatory agencies.

The original 190-901 NH analysis included patients from cohorts in Hamburg, Germany and at Weill Cornell Medical College (WCMC) in New York, USA and was started prior to the initiation of Study 190-201. The NH study 190-901 was subsequently adapted to include patients from the DEM-CHILD cohort, from participating sites in Germany and Italy, also termed Study 190-901 supplementary (45), which will be referred to as Study 190-901 or NH


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from here onwards, unless stated otherwise. These patients were matched to the cerliponase alfa treated patients across the relevant studies according to inclusion criteria using filters (Section B.2.4.4.3).

Study 190-901 assessed multiple parameters including onset of disease, presentation, genotype, rate of progression on the Hamburg and WCMC disease-specific rating scales measuring motor and language function, and MRI findings. An important outcome of the NH analysis was the confirmation of the clinical course of progression of CLN2 disease, in particular, the predictability of loss of function (motor and language) over time as measured by the CLN2 disease rating scale.

The NH data were to be used: (i) to better understand the performance properties of the two CLN2 disease scales (Weill Cornell LINCL Scale and Hamburg Rating Scale [for more detail see Appendix R]), (ii) to evaluate correlations between the scales and independent clinical measures, (iii) to identify other potential clinical outcomes that are relevant and change with disease duration and severity, and (iv) to generate the group of untreated patients to be used for comparison to the treated study population.

#### B.2.3.4.2. Eligibility criteria for 190-901 natural history analysis

Eligibility criteria and summary methods of matching are reported in Section B.2.4.4.3.

### B.2.3.5. Long-term safety studies

Three studies collected long-term safety data:

- The multicentre, US post-marketing, observational, long-term safety **Study 190-501** is designed to evaluate the long-term safety of cerliponase alfa in patients with a confirmed diagnosis of CLN2 disease.

- The expanded access **Study 190-502** was designed to allow access to cerliponase alfa treatment for children with CLN2 disease who were not able to participate in a clinical trial and to collect additional information on safety and tolerability of the treatment in these patients.

- The multicentre, multinational, observational **Study 190-504** is designed to evaluate the long-term safety of cerliponase alfa in patients with a confirmed diagnosis of CLN2 disease. This is a non-interventional post-authorisation safety study (PASS) in European countries.


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Methodology and results for these studies (**Study 190-501, Study 190-502,** and **Study 190-504**) are included in Appendix F.

### B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 15 presents an overview of the key outcomes assessed across the relevant clinical effectiveness evidence, highlighting which outcomes have new or updated data since the original appraisal, and references the applicable results sections of this appraisal for each outcome and trial.


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**Table 15: Outcomes reported in relevant clinical effectiveness studies**

| | Assessment | Summary | 190-201/202 | 190-203 | MAA | 190-501 | 190-502 | 190-504 |
|---|---|---|---|---|---|---|---|---|
| Primary outcome | CLN2 Clinical Rating Scale – ML score | Combined score of the motor and language domains of the CLN2 Clinical Rating Scale (range 0−6). | Sections B.2.6.2.1 – B.2.6.2.3 | Sections B.2.6.3.1 – B.2.6.3.3 | Sections B.2.6.4.1 – B.2.6.4.3 | × | × | × |
| Key secondary outcomes | CLN2 Clinical Rating Scale total score | 4-domain scale (motor, language, seizure and vision). Score per domain ranging from 0–3[†] | Section B.2.6.2.4 | Section B.2.6.3.4 – B.2.6.3.5 | × | × | × | × |
| | Brain MRI[‡] | Descriptive assessment of brain atrophy | Section B.2.6.2.5 | Section B.2.6.3.6 | Section B.2.6.4.4 | × | × | × |
| Patient reported outcomes | PedsQL™ | Generic paediatric QoL questionnaire. Parent/guardian report | Section B.2.6.5.4 | Section B.2.6.5.4 | Section B.2.6.5.4 | × | × | × |
| | EQ-5D-5L | Generic QoL questionnaire. Proxy reported by parents or responsible person | Section B.2.6.5.4 | Section B.2.6.5.4 | Section B.2.6.5.4 | × | × | × |
| | CLN2-QL | Disease-specific QoL scale | Section B.2.6.5.4 | Section B.2.6.5.4 | Section B.2.6.5.4 | × | × | × |
| Other outcomes | Mortality | Reported death(s) | Section B.2.10.1 | Section B.2.10.1 | Section B.2.10.1 | Section B.2.10.1 | Section B.2.10.1 | Section B.2.10.1 |
| | mUBDRS involuntary movement inventory | Measures type, frequency, and severity of common involuntary movements such as myoclonus and dystonia | × | Section B.2.6.5.3 | × | × | × | × |
| | mUBDRS seizure inventory | Measures type and frequency of seizures, and presence of seizure complications in CLN2 patients in the prior 3-month interval | × | Section B.2.6.5.2 | × | × | × | × |
| | Weill Cornell LINCL Scale | 4-domain scale (myoclonus, feeding/swallowing, language and gait). Score per domain ranging from 0–3. | × | × | Section B.2.6.5.3 | × | × | × |
| | Compliance/ adherence | Percentage of dosing compliance | Section B.2.3.1 | Section B.2.3.2 | Section B.2.3.3 | Appendix F | Appendix F | Appendix F |
| | Concomitant medication | List of the most common drugs/supplements used along with the study intervention | Section B.2.3.1 | Section B.2.3.2 | × | Appendix F | Appendix F | Appendix F |


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| | Assessment | Summary | 190-201/202 | 190-203 | MAA | 190-501 | 190-502 | 190-504 |
|---|---|---|---|---|---|---|---|---|
| | ECG, 12-lead | Standard 12-lead ECG, including heart rate, rhythm, intervals, axis, conduction defects and anatomic abnormalities | Section B.2.10.2.2, Appendix F | Section B.2.10.2.2, Appendix F | Section B.2.10.2.2, | Section B.2.10 | Section B.2.10 | Section B.2.10 |
| | EEG, standard | Assessment for epileptiform activity, frequency slowing (focal vs generalised) | Section B.2.6.5.2 | Section B.2.6.5.2 | Section B.2.6.5.2 | × | × | × |
| | ERG | Measures electrical activity of the retina in response to light stimuli | × | × | Appendix O | × | × | × |
| | VA | The Preferential Looking Test is a method of assessing VA in infants and children with limited cognitive function | Appendix O | Appendix O | × | × | × | × |
| | OCT | A non-invasive imaging test of the retina's layers in order to measure their thickness | Appendix O | Appendix O | Appendix O | × | × | × |
| | Denver II developmental screening test | Test designed to monitor infant/preschool-aged children's development. Four general functions covered: personal social, fine motor adaptive, language, and gross motor | Section B.2.6.5.4 | Section B.2.6.5.4 | × | × | × | × |
| | Bayley Scales of Infant Development III | Developmental functioning scale of infants and young children from 1−42 months | × | × | Section B.2.6.4.5 | × | × | × |
| | Wechsler Preschool and Primary Scale of Intelligence | Early childhood intelligence scale | × | × | Section B.2.6.4.5 | × | × | × |
| | Vineland Adaptive Behaviour Scale | Clinical instrument designed to measure adaptive behaviour in individuals from birth through to 90 years of age | × | × | Section B.2.6.4.5 | × | × | × |

Indicates where updates to/new data is described, which was not previously reported in HST12

Indicates not reported

†This outcome was collected as part of the MAA and will be reported in a future MAA report; ‡Reported as an additional outcome of the MAA.

Abbreviations: CLN2, neuronal ceroid lipofuscinosis Type 2; ECG, electrocardiogram; EEG, electroencephalogram; ERG, electroretinogram EQ-5D-5L; EuroQol-5 Dimension 5 Level; ML, motor language; MRI, magnetic resonance imaging; mUBDRS, modified unified Batten disease rating scale; OCT, optical coherence tomography; PedsQL, measurement model for Pediatric Quality of Life Inventory; QoL, quality of life; VA, visual acuity.


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### B.2.4.1. Study 190-201/202

#### B.2.4.1.1. Analysis populations

The analysis populations in Study 190-201/202 are presented in Table 16.

**Table 16: Study 190-201/202 analysis sets**

| Analysis set | Description |
|---|---|
| ITT | The ITT analysis population comprised all study participants from 190-201/202 who received any amount of study drug and report any efficacy results, except: One participant was terminated from 190-201 after a single infusion of study drug and is not included in the ITT population for 190-202. The participant terminated at the parents' request due to the participant's unwillingness to continue with study procedures |
| Study 190-901 ITT analysis population | The 190-901 ITT population comprised the 190-901 participants who satisfied the 190-201 inclusion criterion: Age ≥3 years; and at least one ML score ≥3 points at age ≥3 years |
| Study 190-901 evaluable NH population | The evaluable population included 190-901 participants in ITT population who had at least two CLN2 assessments with values within the range 1–5 points and at least 6 months apart |
| Safety analysis population | The safety analysis population comprised all participants in 190-201/202 who had an ICV reservoir implanted in 190-201 |

Source: Final CSR for 190-202 (44).
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ICV, intracerebroventricular infusion; ITT, intent-to-treat; ML, motor language.

Two sets of analyses were performed during Study 190-201/202, which are referred to as the full and matched sets. The full set compared the 190-201/202 ITT population and the 190-901 ITT NH analysis population (Appendix M). Key analyses of CLN2 scales used the matched set, which was based on 1:1 matching between the 190-201/202 ITT population and 190-901 evaluable NH cohort (Section B.2.4.4).

#### B.2.4.1.2. Participant disposition

Participant disposition is provided in Appendix D.

#### B.2.4.1.3. Sample size

No formal sample size calculations were performed. Sample size for the extension study 190-202 was determined by the number of participants who completed the primary study 190-201; sample size for the primary study was determined on the basis of the ultra-rare nature of CLN2 disease (57).Twenty-three patients completed Study 190-201 and subsequently transitioned into Study 190-202. All 23 participants who completed 48 weeks of treatment in Study 190-201, had at least 48 weeks of additional treatment in Study 190-202. All summaries were descriptive. Given the small sample size of 190-201/202, participants were pooled across all sites for the primary efficacy and safety analyses (44).


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Results could be examined within site on an exploratory basis. All outcomes are reported in the ITT population (n=23).

The sample size estimate was derived from analysis of the NH database. The primary endpoint was assumed to be the within-subject estimate of slope reflecting the rate of decline in the ML score over time (primary outcome). Based on a review of participants from 190-901, it was assumed that untreated patients would decline a mean of 2.0 points per 48 weeks. The actual slopes for rate of change estimates using two different modelling methods were both >2.0 (2.18 and 2.89 per year), but 2.0 per 48 weeks was chosen as a conservative estimate for purposes of comparison for the 190–201 analysis. The primary analysis was assumed to be a one-sample t-test against a fixed-point alternative:

$$H0: \mu BMN\text{-}190 = 2.0$$

$$H1: \mu BMN\text{-}190 \neq 2.0$$

where μBMN-190 represents the population mean rate of decline with treatment with cerliponase alfa.

If treatment resulted in a mean rate of decline of 0.5, with a standard deviation (SD) of 1.8, then 18 evaluable participants were required to achieve 90% power to reject H0 in favour of H1, assuming a two-sided test with significance level $\alpha=0.05$. This was increased to 22 participants to allow for a discontinuation rate of ~20%.

#### B.2.4.1.4. General methodology

The matching of Study 190-201/202 participants to NH controls is outlined in Section B.2.4.4.

**Primary outcome**

The primary outcome of Study 190-201/202 was a responder analysis on the 6-point adapted CLN2 ML scale, which included the following assessments:

- Rate of decline (slope analysis) was provided for this outcome. The rate of decline was calculated as follows:
    - Identify a starting point and an ending point, where a “point” is a bivariate observation comprised of (i) a CLN2 score and (ii) a time point
    - Determine the slope of the line connecting the two points:

Slope = (ending CLN2 score) – (starting CLN2 score)/ (ending date) – (starting date)


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- Calculate the rate of decline as the negative of the line's slope, scaled to a 48-week time period:
  Rate of decline = (–1) × (48 × 7) × slope

- Response was defined as the absence of an unreversed two-point decline or score of zero in CLN2 score by Week 48 (Study Day 340 relative to first 300 mg infusion). An unreversed two-point decline was defined as a decline that had not returned to within 1-point of baseline at the time of the final study ML assessment. The proportion of participants responding by Week 48 was tested against a fixed-point alternative using a 1- sample exact binomial test. The null and alternative hypotheses to be tested were:

  $$H0: pBMN\text{-}190 \leq 0.5$$

  $$H1: pBMN\text{-}190 > 0.5$$

  where pBMN-190 represents the percent responding in the cerliponase alfa-treated population.

  - Time from baseline to first unreversed decline in CLN2 Clinical Rating Scale ML score, and time from baseline to first unreversed two-point decline or total score of zero, were summarised using binomial proportions and Kaplan-Meier (KM) estimates.

**Secondary and exploratory endpoints**

In addition to analysis of the ML scale score, analyses of the rate of decline were also performed for the MLV scale and the total CLN2 scale scores (i.e. MLVS) (44). Analyses were of the change in scale scores from the 300 mg baseline to the last recorded observation.

Brain MRI parameter assessments were also conducted, with results presented descriptively over time and summarised in tabular format by nominal timepoint.

The Denver II Development Scale was administered to assess development milestones and summarised in tabular format by nominal timepoint. QoL was assessed using three different instruments; (i) PedsQL Parent Report for Toddlers, (ii) Parent Family Impact, (iii) CLN2 disease-based QoL. These three QoL instruments, further detailed in Appendix R, include multiple modules, which were scored separately and then added for an overall score. Results were presented descriptively over time and summarised in tabular format by nominal timepoint.


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OCT and VA were assessed to provide additional data, supplementing the vision domain of the CLN2 scale. These outcomes were presented descriptively over time.

EEGs were summarised in terms of the proportion of participants with epileptiform activity and/or frequency slowing, in combination with the activity's location (focal vs. generalised), at baseline and at any time after initiation of study drug. The proportion of participants showing new such activity (defined by the combination of activity and location) relative to baseline was summarised.

#### B.2.4.1.5. Analysis plan

Five interim analyses have been performed in 190-202 using data accrued up to data cut-off dates of 15 October 2015 (interim CSR for Biologics License Application), 03 June 2016 (Day 120 Safety Update), 01 November 2016 (interim CSR update for drug applications), 26 April 2018, and 26 April 2019. Clinical study reports were generated based on two of these interim analyses, with HST12 reporting data from 1st November 2016 interim CSR (17).

### B.2.4.2. Study 190-203

#### B.2.4.2.1. Analysis populations

The sets of analysis populations defined in the trial are presented in Table 17.

**Table 17: Definition of analysis populations Study 190-203**

| Analysis set | Description |
|---|---|
| ITT | The ITT analysis population comprised all study participants from 190-203 who received any amount of study drug and report any efficacy results |
| Study 190-901 evaluable NH population | The evaluable population included 190-901 participants who had at least one assessment ML≥3, and at least two ML assessments with values within the range 1–6 points and at least 6 months apart |
| Safety analysis population | The safety analysis population comprised all participants in 190-203 who had an ICV reservoir implanted |

Source: Study 190-203 CSR, 2023 (19)
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ICV, intracerebroventricular infusion; ITT, intent-to-treat; ML, motor language.

Two sets of efficacy analyses were performed during Study 190-203, which are referred to as the full and matched sets. The full set compared the 190-203 ITT (N=14) population and the 190-901 evaluable population. The matched set was based on 3:1 matching between the 190-203 ITT population and 190-901 evaluable cohort, outlined in Section B.2.4.4.

#### B.2.4.2.2. Participant disposition

Participant disposition is provided in Appendix D.


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#### B.2.4.2.3. Sample size

Fourteen participants were enrolled. Sample size was determined based on clinical judgment and statistical power was not a consideration.

#### B.2.4.2.4. General methodology

Cerliponase alfa was administered by ICV infusion every 14 days (+3 days) according to the participant's age:

- Birth to <6 months: 100 mg
- 6 months to <1 year: 150 mg
- 1 year to <2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- ≥2 years: 300 mg

Efficacy and safety analyses were for the full group of participants, regardless of dose level received. The efficacy analyses were based on the ITT population. Follow-up and assessment of the CLN2 Clinical Rating Scale was planned for each participant for a total of 169 weeks, including the 145-week treatment period and 24-week safety follow up period. Efficacy analyses of CLN2 rating scales included comparison with a NH database (190-901) based on matching.

Safety and efficacy variables were summarised descriptively. Descriptive statistics included participant count, mean, median, SD, minimum, and maximum for continuous variables and count and percentage for categorical variables. The 95% confidence interval (CI) for mean and percentiles were included, if appropriate.

**Primary outcome**

The primary outcome in study 190-203 was the CLN2 Clinical Rating Scale ML score, the methodology of which is as described for Study 190-201/202 in Section B.2.4.1.4.

In addition, time to disease manifestation was assessed for pre-symptomatic participants (MLVS=12). Subsequent disease manifestation was defined as post-baseline consecutive measurements of M, L, V, or S scores <3, measured at least 22 days apart. The time of disease manifestation was defined as the time of the first of the two measurements demonstrating the deficit. This was analysed using KM and Cox proportional hazards model of time.


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**Secondary and exploratory outcomes**

In addition to the secondary endpoints covered in Study 190-201/202 (Section B.2.4.1.4), the modified Unified Batten Disease Rating Scale (mUBDRS) Involuntary Movement Inventory, and mUBDRS seizure inventory were assessed. Using a 4-point Likert Scale (0–3) a total score was generated as a sum of all items over the number of items answered on all scales. Lower scores indicate higher frequency, severity, or pronounced presence of involuntary movements, or higher frequency seizures and higher presence of seizure complications. Results were presented descriptively over time.

#### B.2.4.2.5. Analysis plan

No formal interim analyses were planned. Analyses were produced for a biologics licensing application to FDA based on visits through 01 November 2016. Analyses were produced for purpose of regulatory reporting and congress presentations based on data through 26 April in 2018, 2019, 2020, and 2021. An interim clinical study report based on visits up to 26 April 2020 was produced at the request of the Paediatric Committee (PDCO). Final analyses were presented in a final CSR, which included data up to the completion date 20th April 2022.

### B.2.4.3. MAA data

#### B.2.4.3.1. Analysis populations

The sets of analysis populations defined in the DCA are presented in Table 18. Clinical outcomes for cerliponase alfa treated populations were assessed for the full analysis set (FAS) of the MAA cohort, and for the MAA new starter patient set.

**Table 18: Definition of analysis populations MAA data**

| Analysis set | Description |
|---|---|
| FAS | MAA cohort, consisting of both ex-trial MAA patients and MAA new starter patients |
| Ex-trial MAA patients | Patients who started cerliponase alfa treatment as part of a clinical trial or the extended access programme and who continue to receive treatment under the terms of the MAA |
| MAA new starter patients | Patients who have never received cerliponase alfa treatment and start treatment at the age of 3 years and older under the terms of the MAA |

Source: MAA SAP, 2023 (71)
Abbreviations: FAS, full analysis set; MAA, managed access agreement; Tx, treatment.

#### B.2.4.3.2. Participant disposition

Participant disposition is provided in Appendix D.


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#### B.2.4.3.3. Sample size

A total of 35 participants were enrolled: 11 ex-trial patients and 24 MAA new starter patients. Sample size was determined based on clinical judgment and statistical power was not a consideration.

#### B.2.4.3.4. General methodology

Cerliponase alfa was administered in line with the SmPC (24).

Efficacy analyses were for the full group of participants, regardless of dose level received. The efficacy analyses were based on the MAA FAS and the MAA new starter patient populations. Follow-up and assessment of the CLN2 Clinical Rating Scale was planned for each participant every six months, up to five years. Efficacy analyses of CLN2 Clinical Rating Scales included comparison with a NH database (190-901) based on matching (Section B.2.4.4.3).

Efficacy variables were summarised descriptively. Descriptive statistics included participant count, mean, median, SD, minimum, and maximum for continuous variables and count and percentage for categorical variables. The 95% CI for mean and percentiles were included, if appropriate.

**Key outcomes**

Key outcomes collected during the MAA evaluation period are outlined in Table 19.


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**Table 19: Summary of key outcomes assessed across the MAA evaluation period**

| Outcome | | Detail | Treatment baseline† | MAA enrolment‡ | Month‡‡ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
| Clinical assessments | CLN2 Clinical Rating Scale | M, MLV, and MLVS score<br>• Rate of decline (slope analysis)¶<br>• Responder analysis (time to unreversed decline)¶<br>• Descriptive statistics of changes from baseline§ | X | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Weill Cornell LINCL Scale | Summary statistics will be provided for the Full Analysis Set and subgroups for all MAA assessment periods. Mean (SD) change from baseline and mean (SD) inter-assessment change will also be provided. Results will be presented by individual domain (myoclonus, feeding/swallowing, language, and gait) and by total score (sum of domain scores). | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | ECG, 12-lead | Proportion of patients/assessments with reported cardiac abnormalities (binary record – yes or no) and/or clinically significant abnormalities (binary record – yes or no) | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | EEG, standard | Proportion of patients/assessments with reported epileptiform activity (binary record – yes or no) and/or frequency slowing (binary record – yes or no) provided | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Brain MRI | Change in brain volumetry as provided in MRI reports reported where applicable and available | × | ✓ | ✓ | ✓ | × | ✓ | × | ✓ | × | ✓ |
| VA assessments | ERG | • Change over time in OCT, VEP and ERG results reported where applicable and available<br>• Mean age at first report of undetectable response reported where available | × | ✓ | ✓ | ✓ | × | ✓ | × | ✓ | × | ✓ |
| | OCT | | × | ✓ | ✓ | ✓ | × | ✓ | × | ✓ | × | ✓ |
| | VEP | | × | ✓ | ✓ | ✓ | × | ✓ | × | ✓ | × | ✓ |
| PROs†† | PedsQL™ | • Scores (by dimension, and total) will be descriptively summarised<br>• Summary statistics of mean score, dimension scores and total score for baseline and follow-up<br>• Change from baseline | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |


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| Outcome | | Detail | Treatment baseline† | MAA enrolment‡ | Month‡‡ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
| | EQ-5D-5L | • Summary statistics and absolute change will be provided for the VAS score, each of the five dimension scores (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and index value (calculated using the UK crosswalk value set)<br>• EQ-5D-5L index scores summarised by ML score (mean, median, standard deviation, and range value). Groupings may be determined by data availability | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | CLN2-QL | • Scores (by dimension, and total) will be descriptively summarised<br>• Summary statistics of mean score, dimension scores and total score will be provided for baseline and follow-up. Change from baseline will also be provided | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Neurodevelopmental assessments | BSID-III | • Summary statistics of total score and domain scores (the cognitive scale, the language scale and the motor scale) provided for baseline and follow-up and by patient age<br>• Change from baseline provided | × | ✓ | ✓ | ✓ | × | ✓ | × | ✓ | × | ✓ |
| | WPPSI-IV | Summary statistics of total score for baseline and follow-up and by patient age. Change from baseline also be provided | × | ✓ | ✓ | ✓ | × | ✓ | × | ✓ | × | ✓ |
| | VABS | • For patients <7 years old: Summary statistics of the four main domains (communication, daily living skills, socialization, and motor skills) provided for baseline and follow-up and by patient age. Change from baseline also provided<br>• For patients >7 years: Summary statistics of three domains (communication, daily living skills and socialization) provided for baseline and follow-up and by patient age. Change from baseline also provided | × | ✓ | ✓ | ✓ | × | ✓ | × | ✓ | × | ✓ |

Source: MAA SAP, 2023 (71).
†Ex-trial patients only (190-201/202, 190-203, 190-502). All data available between treatment baseline and MAA enrolment will be included in the analyses; ‡Equal to treatment baseline for MAA new starter patients; ¶Methodology described in Section B.2.4.1.4; §For new MAA starter patients only; ††Available for patients transferring from 190-201/202 and 190-203 only; ‡‡For assessments that are missed or abbreviated due to full vision loss, centres were requested to add relevant commentary in the data entry form.
Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, 3rd Ed.; CLN2, neuronal ceroid lipofuscinosis type 2; CLN2-QL, CLN2 Disease Based Quality of Life; ECG, electrocardiogram; EEG, electroencephalogram; ERG, electroretinogram; LINCL, late infantile neuronal ceroid lipofuscinoses; M, motor, MAA, managed access agreement; ML, motor language; MLV, motor language vision; MLVS, motor language vision seizure; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PedsQL, Paediatric Quality of Life Inventory; PRO, patient reported outcome; WPPSI-IV, Wechsler Preschool & Primary Scale of Intelligence, 4th Ed.; VA, visual acuity; VAS, visual analogue scale; VABS, Vineland Adaptive Behaviour Scales; VEP, visual evoked potential.


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#### B.2.4.3.5. Analysis plan

The analysis included MAA data for the period November 2019–September 2023 inclusive. Relevant data from Study 190-201/202, Study 190-203, and 190-504 were included in supportive analyses of ex-trial MAA patients where appropriate and available (71).

### B.2.4.4. Natural history controls (Study 190-901)

#### B.2.4.4.1. Participant disposition

Participant disposition is provided in Appendix D.

#### B.2.4.4.2. Sample size

Forty-two (of which 17 were used in the 1:1 matched analysis of Study 190-201/202; 29 were used in the 3:1 matched analysis of Study 190-203, 26 were used in the 1:1 matched analysis of the MAA FAS, and 17 were used in the 1:1 matched analysis of the MAA new starter cohort).

#### B.2.4.4.3. General methodology

At the time that BioMarin received the initial DEM-CHILD data transfer (February 2015), two sites had clinical data on a total of 74 CLN2 patients (63 from the Hamburg site and 11 from the Verona site) with CLN disease. Of these 74 patients, 58 had at least one recorded ML score. Several filters were applied to the 58 patients to align or match participants with the patient population in Study 190-201, Study 190-203, and the MAA including:

- At least 2 evaluations of CLN2 Clinical Rating Scale at age of ≥36 months
- At least 1 score of CLN2 Clinical Rating Scale ≥3
- At least 2 scores of CLN2 Clinical Rating Scale between 1 and 5
- At least 1 rating of CLN2 Clinical Rating Scale ≥6 months after first rating.

The purpose of applying these filters was to include patients for whom data were available on progression of disease after matching to patients on the basis of CLN2 Clinical Rating Scale score and age at baseline in the studies examining cerliponase alfa treated participants.

This method of matching was specified prior to performing any efficacy analyses and was designed to allocate the maximal number of participants to a unique 190-901 patient (no sharing). The follow-up assessments for Study 190-901 patients were included up to the


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longest duration that is less than or equal to the full 300 mg dosing duration of the matched patient. The goal of this methodology was to provide an equal comparison between the two populations over a similar period, starting at the same point with respect to key prognostic variables. Table 20 presents the clinical effectiveness studies which include analyses of participants matched to NH, including their respective matching criteria at baseline.

**Table 20: NH matching criteria for relevant clinical effectiveness studies**

| 190-201/202 | 190-203 | MAA | DEM-CHILD-RX |
|---|---|---|---|
| • Equal ML score<br>• Age within 3 months<br>• Genome with equal number of common alleles (c.622C-T, c.509.1G-C) | • Equal ML score<br>• Age within 3 months<br>• Genome with equal number of common alleles (c.622C-T, c.509.1G-C) | • Equal ML score<br>• Age within 3 months | • Equal ML score<br>• Age within 12 months |

Sources: Schulz et al, 2024 (57); Study 190-203 CSR, 2023 (19); MAA SAP, 2023 (71); DEM-CHILD-RX SAP, 2022 (72).
Abbreviations: MAA, Managed access agreement; ML, motor language; NH, natural history.

The primary efficacy measure across the relevant clinical effectiveness trials was the change in CLN2 Clinical Rating Scale score from baseline, with a primary analysis comparison of the treatment effect of cerliponase alfa to the predicted mean decline of two-points per 48 weeks in the matched NH population. Treatment effect was assessed by comparing the number of patients who did not experience an unreversed two-point decline by Week 48 in the relevant trials with that in the relevant matched NH controls using a Fisher exact test. This was a conservative estimate of the within-subject change based on review of participants from NH databases. For this analysis, the proportion of participants who did not experience an unreversed two-point decline by Week 48 was tested against a fixed proportion of 0.50 using a one sample exact binomial test. The results were also presented as KM estimates (e.g. time to unreversed two-point decline) and compared using a Cox proportional hazards model. Slopes (the rate of decline in the CLN2 disease rating scale in points per 48 weeks) were also compared both for cerliponase alfa treated and untreated patients in the overall NH population using a two-sample t-test, with adjustment to accommodate unequal variances. The rate of decline was estimated for each patient over the period of decline (i.e. from the first score that was <6 to the last score that was >0).

**Matching of NH to 190-201/202 – Overview**

The analytical matching methodology was defined to align with the planned analyses for the Study 190-201 and was refined in discussion with regulatory agencies. Data were re-


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analysed to focus on a NH matched population enrolled in Study 190-201/202. The primary analysis was based on a 1:1 matching algorithm. Analyses were performed on the treatment period starting from the baseline for the 300 mg stable dose period. The base case analyses were on the ITT population.

**Matching of NH to 190-203 – Overview**

The matching was based on a 3:1 matching algorithm, of the NH evaluable population and the Study 190-203 ITT population and was included as the main comparative analysis set out in the study protocol.

NH participants were weighted inversely to the number of NH participants matched to a given Study 190-203 participant. The weights for three, two, and one NH participant(s) matched to a given Study 190-203 participant were 1/3, 1/2, and 1, respectively. The weights were normalised to sum to the total number of NH participants matching to Study 190-203 participants. Study 190-203 and NH participants who were not matched were excluded from matched analyses. Of note, presentation of categorical data from matched NH participants (e.g. number of male and female participants) could have a non-integer value since the tabulations were based on weighted matching.

**Matching of NH to the MAA cohort – Overview**

Analyses of both the MAA FAS and MAA new starter cohorts were based on a 1:1 matching algorithm. As the MAA did not collect any patient genomic data, patients were not matched based on an equal number of common alleles.

## B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of Study 190-201, Study 190-202, Study 190-203, the MAA data, and Study 190-901 is presented in Table 21, Table 22, Table 23, Table 24, and Table 25, respectively. Please note that critical appraisal of the other studies included by the SLR are provided in Appendix D.


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**Table 21: Critical appraisal of Study 190-201**

| Study name | Study 190-201; NCT01907087 (50, 67-69) | |
|---|---|---|
| Study question | Response yes/no/not clear/N/A) | How is the question addressed in the study? |
| Was the cohort recruited in an acceptable way? | Yes | Patients were recruited according to pre-defined eligibility criteria. |
| Was the exposure accurately measured to minimise bias? | Yes | Patients were administered defined doses of cerliponase alfa at set time intervals (every other week). |
| Was the outcome accurately measured to minimise bias? | Yes | Patients were assessed at regular intervals after treatment initiation and their disease progression evaluated by using a defined scoring system and examination of a set of clinical parameters (please see Appendix R for more details on the CLN2 Clinical Rating Scale). |
| Have the authors identified all important confounding factors? | Not clear | Insufficient information provided. |
| Have the authors taken account of the confounding factors in the design and/or analysis? | Not clear | 1:1 matching of untreated patients from Study 190-901 with patients from Study 190-201/202 was performed, to provide an equal comparison between the two populations over a similar period of time and starting at the same point with respect to key prognostic variables (i.e. age, genotype, CLN2 Clinical Rating score) |
| Was the follow-up of patients complete? | Yes | After study completion patients were enrolled in a long-term follow-up study (Study 190-202) |
| How precise (for example, in terms of CI and p values) are the results? | Yes | Results were accompanied by the description of Cis and p-values where applicable and were otherwise comprised of mean values with SD |

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence; 12 questions to help you make sense of a cohort study.
Abbreviations: CI, confidence intervals; CLN2, neuronal ceroid lipofuscinosis type 2; N/A, not applicable; SD, standard deviation.


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**Table 22: Critical appraisal of Study 190-202**

| Study name | Study 190-202; NCT02485899 (50, 57, 64, 68, 69) | |
|---|---|---|
| Study question | Response yes/no/not clear/N/A) | How is the question addressed in the study? |
| Was the cohort recruited in an acceptable way? | Yes | Patients were recruited according to pre-defined eligibility criteria |
| Was the exposure accurately measured to minimise bias? | Yes | Patients were administered defined doses of cerliponase alfa at set time intervals (every other week) |
| Was the outcome accurately measured to minimise bias? | Yes | Patients were assessed at regular intervals after treatment initiation and their disease progression evaluated by using a defined scoring system and examination of a set of clinical parameters |
| Have the authors identified all important confounding factors? | Not clear | Insufficient information provided |
| Have the authors taken account of the confounding factors in the design and/or analysis? | Not clear | 1:1 matching of untreated patients from Study 190-901 with patients from Study 190-201/202 was performed, to provide an equal comparison between the two populations over a similar period of time and starting at the same point with respect to key prognostic variables (i.e. age, genotype, CLN2 Clinical Rating score) |
| Was the follow-up of patients complete? | Yes | Study was completed December 2020 |
| How precise (for example, in terms of CI and p values) are the results? | Yes | Results were accompanied by the description of Cis and p-values where applicable and were otherwise comprised of mean values with SD |

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence; 12 questions to help you make sense of a cohort study.
Abbreviations: CI, confidence intervals; CLN2, neuronal ceroid lipofuscinosis type 2; N/A, not applicable; SD, standard deviation.


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**Table 23: Critical appraisal of Study 190-203**

| Study name | 190-203; NCT02678689 (65) | |
|---|---|---|
| Study question | Response yes/no/not clear/N/A) | How is the question addressed in the study? |
| Was the cohort recruited in an acceptable way? | Yes | Patients were recruited according to pre-defined eligibility criteria. |
| Was the exposure accurately measured to minimise bias? | Yes | Patients were administered defined doses of cerliponase alfa at set time intervals (every other week). |
| Was the outcome accurately measured to minimise bias? | Yes | Patients were assessed at regular intervals after treatment initiation and their disease progression evaluated by using a defined scoring system and examination of a set of clinical parameters |
| Have the authors identified all important confounding factors? | Not clear | Insufficient information provided |
| Have the authors taken account of the confounding factors in the design and/or analysis? | Not clear | 3:1 matching of untreated patients from Study 190-901 with patients from Study 190-203 was performed, to provide an equal comparison between the two populations over a similar period of time and starting at the same point with respect to key prognostic variables (i.e. age, genotype, CLN2 Clinical Rating score) |
| Was the follow-up of patients complete? | Yes | Study was completed in April 2022 |
| How precise (for example, in terms of CI and p-values) are the results? | Yes | Results were accompanied by the description of Cis and p-values where applicable and were otherwise comprised of mean values with SD |

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence; 12 questions to help you make sense of a cohort study.
Abbreviations: CI, confidence intervals; CLN2, neuronal ceroid lipofuscinosis type 2; N/A, not applicable; SD, standard deviation.


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**Table 24: Critical appraisal of MAA**

| Study name | MAA (71) | |
|---|---|---|
| Study question | Response yes/no/not clear/N/A) | How is the question addressed in the study? |
| Was the cohort recruited in an acceptable way? | Yes | Patients were treated based on pre-defined starting and/or maintenance eligibility criteria |
| Was the exposure accurately measured to minimise bias? | Yes | Patients were administered defined doses of cerliponase alfa at set time intervals (every other week) |
| Was the outcome accurately measured to minimise bias? | Yes | Patients were assessed at regular intervals after treatment initiation and their disease progression evaluated by using a defined scoring system and examination of a set of clinical parameters |
| Have the authors identified all important confounding factors? | Not clear | Insufficient information provided |
| Have the authors taken account of the confounding factors in the design and/or analysis? | N/A | 1:1 matching of untreated patients from Study 190-901 with MAA FAS, and MAA new starter cohort patients was performed, to provide an equal comparison between the populations over a similar period of time and starting at the same point with respect to key prognostic variables (i.e. age, CLN2 Clinical Rating score) |
| Was the follow-up of patients complete? | N/A | No. Under the MAA, cerliponase alfa treatment and data capture will continue until November 2024 |
| How precise (for example, in terms of CI and p values) are the results? | Yes | Results were accompanied by the description of CIs and p values where applicable and were otherwise comprised of mean values with SD |

Abbreviations: CI, confidence intervals; CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; MAA, managed access agreement; N/A, not applicable; SD, standard deviation.


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**Table 25: Critical appraisal of Study 190-901**

| Study name | Study 190-901 (25, 45) | |
|---|---|---|
| Study question | Response yes/no/not clear/N/A) | How is the question addressed in the study? |
| Was the cohort recruited in an acceptable way? | Yes | Patients from the DEM-CHILD database were selected based on key eligibility criteria from Study 190-201/202 |
| Was the exposure accurately measured to minimise bias? | N/A | Study 190-901 was a NH study of untreated patients |
| Was the outcome accurately measured to minimise bias? | Yes | Patients were assessed and their disease progression evaluated by using a defined scoring system and examination of a set of clinical parameters via the CLN2 Clinical Rating Scale |
| Have the authors identified all important confounding factors? | Not clear | Insufficient information provided |
| Have the authors taken account of the confounding factors in the design and/or analysis? | Yes | 1:1 matching of untreated patients from Study 190-901 with patients from Study 190-201/202, Study 190-203 and the MAA cohort was performed, to provide an equal comparison between the populations over a similar period of time and starting at the same point with respect to key prognostic variables |
| Was the follow-up of patients complete? | N/A | Study 190-901 was a NH study based on a retrospective database review |
| How precise (for example, in terms of CI and p values) are the results? | Yes | Results were accompanied by the description of Cis and p values where applicable and were otherwise comprised of mean values with SD |

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence; 12 questions to help you make sense of a cohort study.
Abbreviations: CI, confidence intervals; CLN2, neuronal ceroid lipofuscinosis type 2; N/A, not applicable; NH, natural history; SD, standard deviation.


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## B.2.6. Clinical effectiveness results of the relevant studies

### B.2.6.1. Overview

This section presents newly captured cerliponase alfa clinical efficacy data. Since the original NICE HST submission in 2017 (14), Study 190-201/202 and Study 190-203 have been completed and their clinical efficacy data are presented in Section B.2.6.2 and B.2.6.3, respectively. The newly captured MAA clinical effectiveness data are presented in Section B.2.6.4, DEM-CHILD-RX and Study 190-801 Wave 1 supplementary data are presented in Appendix P and Appendix Q, respectively. Note that Study 190-201 efficacy data are included in Appendix O, and the NH control (Study 190-901) results are presented in Appendix M.

### B.2.6.2. Efficacy outcomes of Study 190-201/202

In total for the combined Study 190-201/202, the mean treatment duration for the ITT population was 272 weeks; all 23 participants had at least 162 weeks of cerliponase alfa treatment at the 300 mg dose (57).

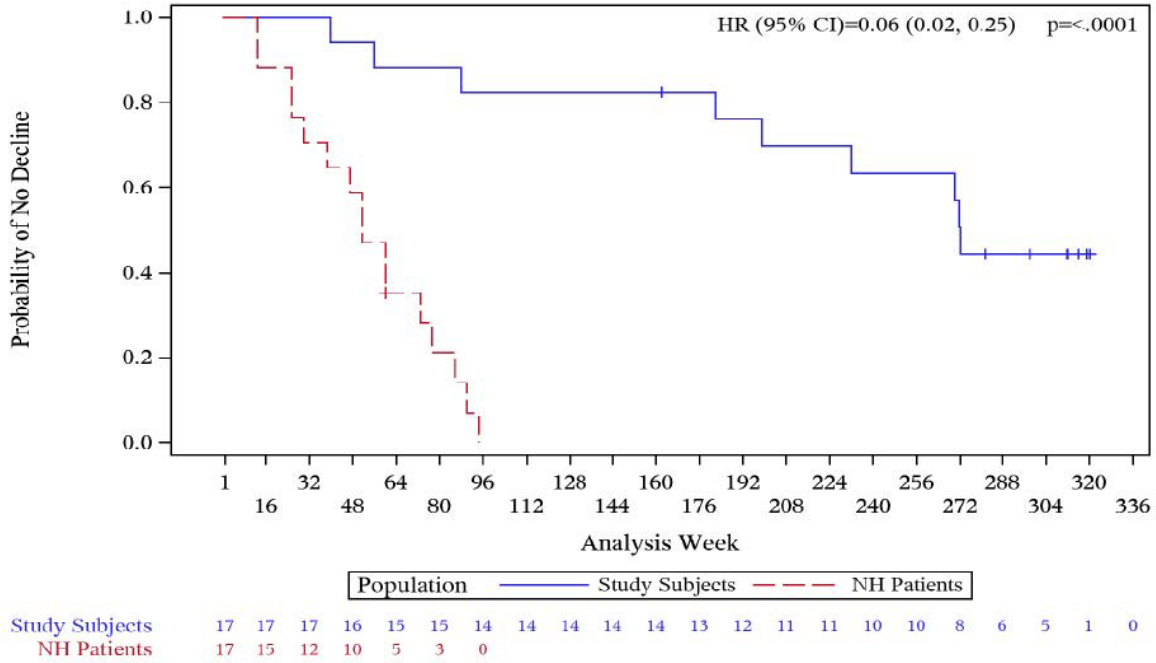
Seventeen of 23 participants from 190-201/202 met criteria for matching with NH controls (44). The 190-201/202 and NH groups were well balanced, with the slight exception of sex. In the NH evaluable population, 7 participants (41%) were female, and 10 participants (59%) were male.

#### B.2.6.2.1. Time to unreversed two-point decline or score of zero in ML score

There was a statistically significant difference in the 190-201/202 participants time to first unreversed two-point decline or score of zero in ML score, as compared with NH controls (Figure 4) (44). This was demonstrated by a hazard ratio (HR) 0.06 (95% CI: 0.02, 0.25; $p<0.0001$), with cerliponase alfa treated participants an estimated 94% less likely than matched NH participants to experience an unreversed two-point decline or score of zero in ML scale. The median time to event was 5.3-fold later in 190-201/202 treated participants as compared with NH controls (272 vs 51 weeks, respectively).


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**Figure 4: Time to first unreversed 2-point decline or score of 0 in ML score (1:1 matched NH and 190-201/202 population, 300 mg dosing period)**




Source: Final CSR for 190-202 (44).
Note, an unreversed 2-point decline is any decline of 2 points or more that had not reversed to a 1-point decline (or better) at the last recorded observation. An unreversed score of 0 is a decline of 0 that had not increased to a score > 0 at last recorded observation. Analysis Day 1 is the date of the first 300 mg infusion in 190-201. The Cox model includes baseline ML score and baseline age as continuous covariates and genotype (common alleles) and sex as categorical covariates.
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; ML, motor language; NH, natural history.

The treatment effect was analysed considering the participants who did not experience an unreversed decline of 2 points. As also presented in HST12, Table 26 presents the 48-week analysis, where 91% (20/22) of participants in 190-201/202 did not experience an unreversed two-point decline, compared with 45% (10/22) in the matched NH population. The estimated difference in proportion was 46% (p=0.0028). The updated final analysis demonstrated that the benefit of cerliponase alfa is maintained up to 289 weeks of follow-up, with 47% (8/17) of participants that did not experience an unreversed two-point decline compared with 6% (1/17) in the matched NH population. The estimated difference in proportion was 41% (p=0.0003).


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**Table 26: Analysis of treatment effect in 1:1 matched controls**

| | Study 190-201/202 (n=22) | NH (n=22) | Rate difference | Two sided p-value |
|---|---|---|---|---|
| **48 weeks of follow-up (presented in HST12)** | | | | |
| n | 22 | 22 | | |
| Absence of unreversed 2-point decline (positive) | 20 (91%) | 10 (45%) | 46% | 0.0028 |
| Presence of unreversed 2-point decline (negative) | 2 (9%) | 12 (55%) | | |
| **289 weeks of follow-up** | | | | |
| n | 17 | 17 | | |
| Absence of unreversed 2-point decline (positive) | 8 (47%) | 1 (6%) | 41% | 0.0003 |
| Presence of unreversed 2-point decline (negative) | 9 (53%) | 16 (94%) | | |

Source: Interim CSR for 190-202 (17); Final CSR for 190-202 (44).
Abbreviation: NH, natural history.

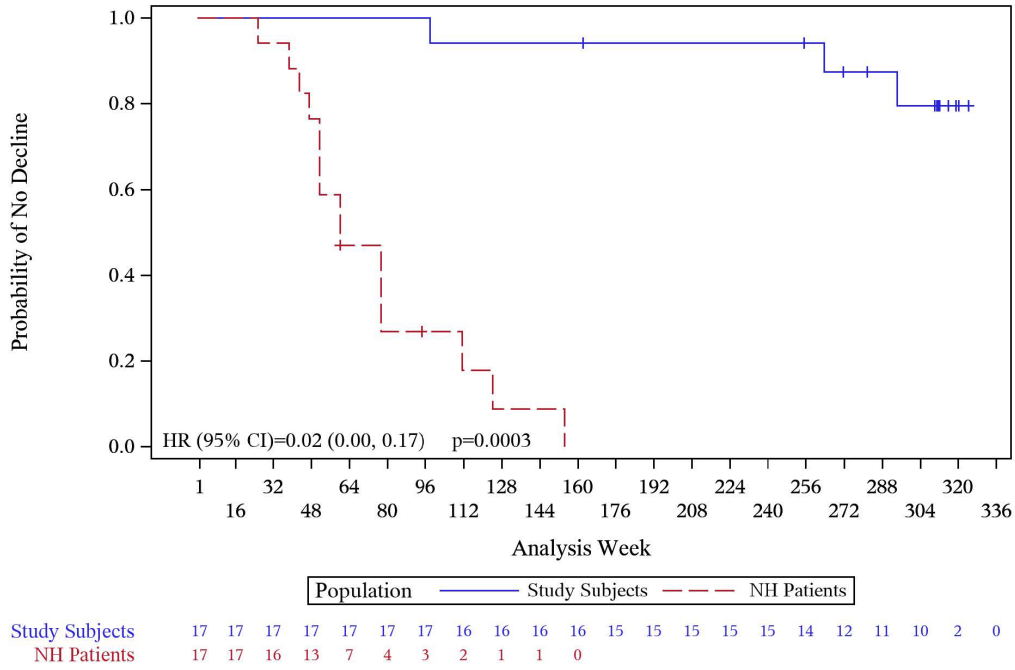
### Time to first unreversed two-point decline or score of zero in individual motor and language domains

The strong cerliponase alfa treatment effect was seen in the individual motor and language domains. Observing individual domain KM curves (Figure 5), events with early onset tended to be language events. Each domain displayed a strong treatment effect, as demonstrated by the motor score HR of 0.02 (95% CI: 0.00, 0.17; p=0.0003), and language HR of 0.11 (95% CI: 0.03, 0.41; p=0.0011). Treatment did not appear to alter the order of disease symptom progression. From the known NH of CLN2, an initial language delay and decline typically occur before the onset of the ataxia and loss of ambulation.

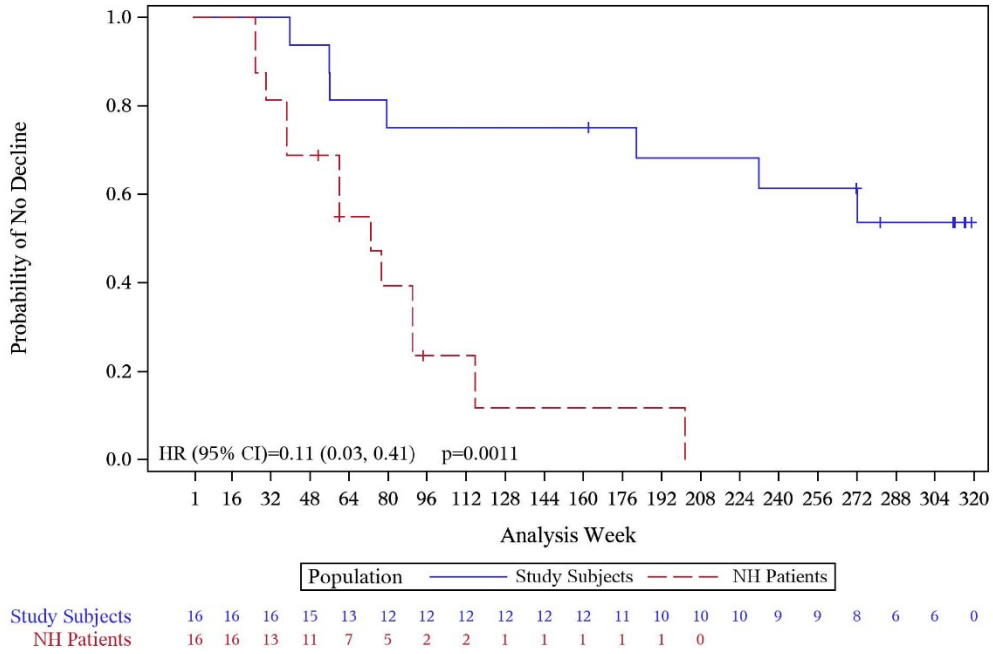

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**Figure 5: Time to first unreversed 2-point decline or score of 0 in motor, and language domains (1:1 matched NH and 190-201/202 population, 300 mg dosing period)**

**A**




**B**




Source: Final CSR for 190-202 (44).
A) Time to first unreversed 2-point decline or score of 0 in individual motor domain
B) Time to first unreversed 2-point decline or score of 0 in individual language domain.
Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; ITT, intent-to-treat; NH, natural history.


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#### B.2.6.2.2. Rate of decline in ML score

HST12 presented the rate of decline of the CLN2 Clinical Rating Scale per 48-week time period from Study 190-201/202 and 1:1 matched NH controls (Table 27). The mean rate of decline was 0.53 vs 2.06 points per 48 weeks in treated participants vs matched NH controls, respectively, a highly statistically significant difference (p<0.0001) and no overlap in the 95% CIs. The final analysis, with an additional 49 months of follow-up, showed that the difference in rate of decline was maintained between treated participants and NH controls.

**Table 27: ML scale – Rate of decline (1:1 matched NH and 190-201/202 population, 300 mg dosing period)**

| Rate of Decline (Points/48 weeks) | 190-201/202 | NH | Difference (NH–190-202) | Two-sided p-value |
|---|---|---|---|---|
| **48 weeks of follow-up (presented in HST12)** | | | | |
| **ML total score** | | | | |
| n | 22 | 22 | | |
| Mean (SD) | 0.53 (0.737) | 2.06 (1.379) | 1.53 | <0.0001 |
| (SE) | | | 0.333 | |
| Median | 0.27 | 2.36 | | |
| 25th, 75th Percentile | 0.00, 0.99 | 1.02, 3.20 | | |
| Min, Max | –0.61, 2.02 | 0.00, 4.98 | | |
| 95% CI | 0.20, 0.86 | 1.45, 2.68 | 0.85, 2.21 | |
| **289 weeks of follow-up (final analysis)** | | | | |
| **ML total score** | | | | |
| n | 17 | 17 | | |
| Mean (SD) | 0.42 (0.569) | 1.92 (1.318) | 1.51 | 0.0003 |
| (SE) | | | 0.348 | |
| Median | 0.30 | 1.87 | | |
| 25th, 75th Percentile | 0.15, 0.31 | 0.93, 2.24 | | |
| Min, Max | 0.00, 2.18 | 0.00, 4.98 | | |
| 95% CI | 0.12, 0.71 | 1.24, 2.60 | 0.78, 2.23 | |

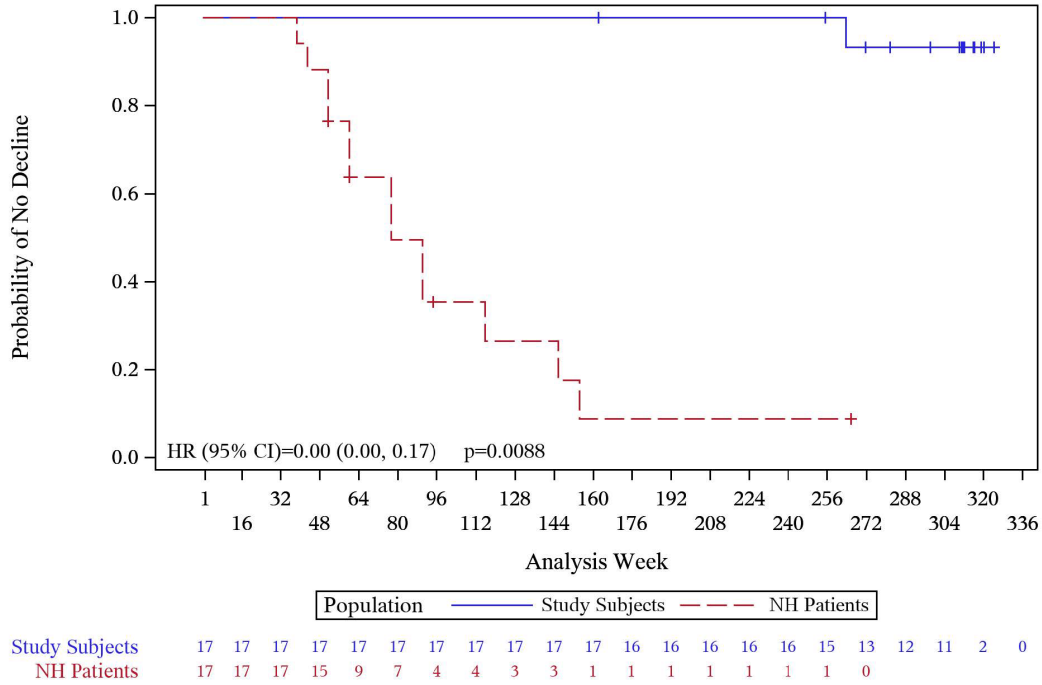
Sources: Study 190-201/202 Interim CSR, 2017 (17); Final CSR for 190-202 (44).
Abbreviations: CI, confidence interval; NH, natural history; SD, standard deviation; SE, standard error.

#### B.2.6.2.3. Time to ML score of zero

The event of unreversed ML score of zero is an event captured in longer term follow-up and represents the most severe/progressed state of the disease as captured by the ML scale. Matched 190-201/202 participants were less likely than NH controls to have an unreversed decline to a score of zero in ML score (HR: 0.00; 95% CI: 0.00, 0.17; p=0.0088). The median time to unreversed ML score of zero in the matched set was not reached among treated participants and was 77 weeks among NH controls.


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**Figure 6: Time to score of 0 in ML score (1:1 matched NH and 190-201/202 population, 300 mg dosing period)**




Source: Final CSR for 190-202 (44).
Note, an unreversed score of 0 is a decline of 0 that had not increased to a score >0 at last recorded observation.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; ML, motor language; NH, natural history.

### B.2.6.2.4. Change in CLN2 Clinical Rating Scale score

In addition to the rate of decline analysis, a descriptive review of the ML scale was performed. Results were calculated as the difference between the result at baseline and at each post baseline study visit.

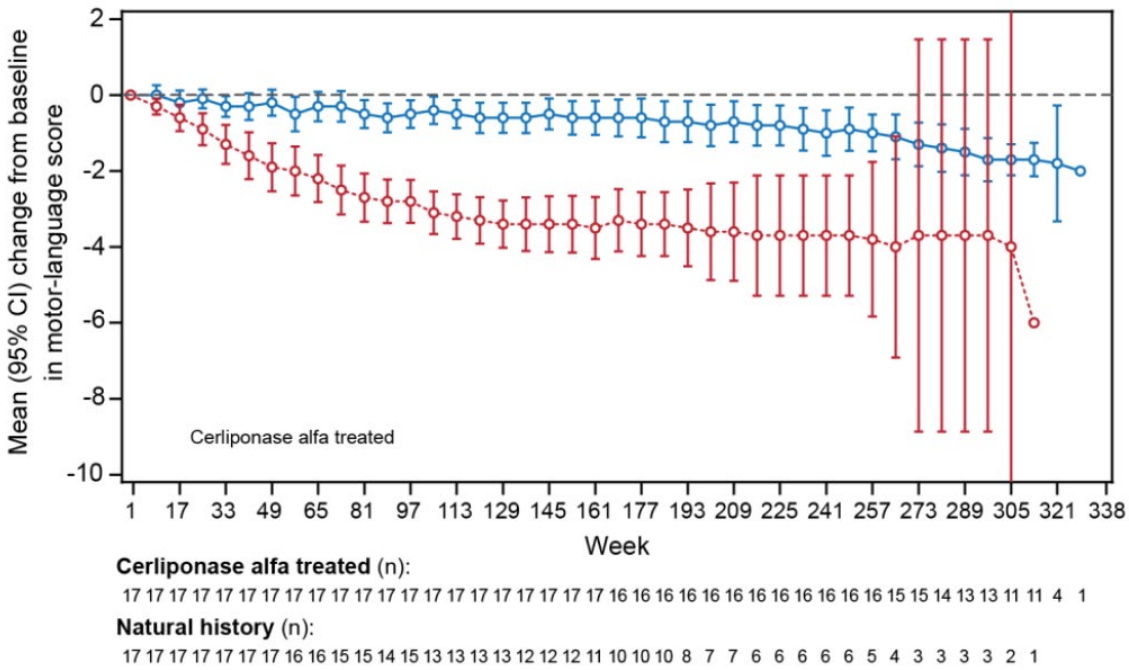
The observed trend for matched participants in 190-201/202 was stability of ML scores from baseline to end of study. There was a clear and sustained separation from matched NH controls post baseline. The NH participants declined in ML score at a faster rate than matched 190-201/202 ITT participants, reflecting the natural progression of CLN2 disease (Figure 7A). The 17 matched 190-201/202 participants lost a total of 26 ML points, compared with 53 ML points lost by the 17 matched NH participants.

The stabilisation of the score across all domains can also be seen by comparing the mean change from baseline score for cerliponase alfa treated participants with all evaluable participants in the NH control population for ratings that include vision and seizures in addition to motor and language (Figure 7B).

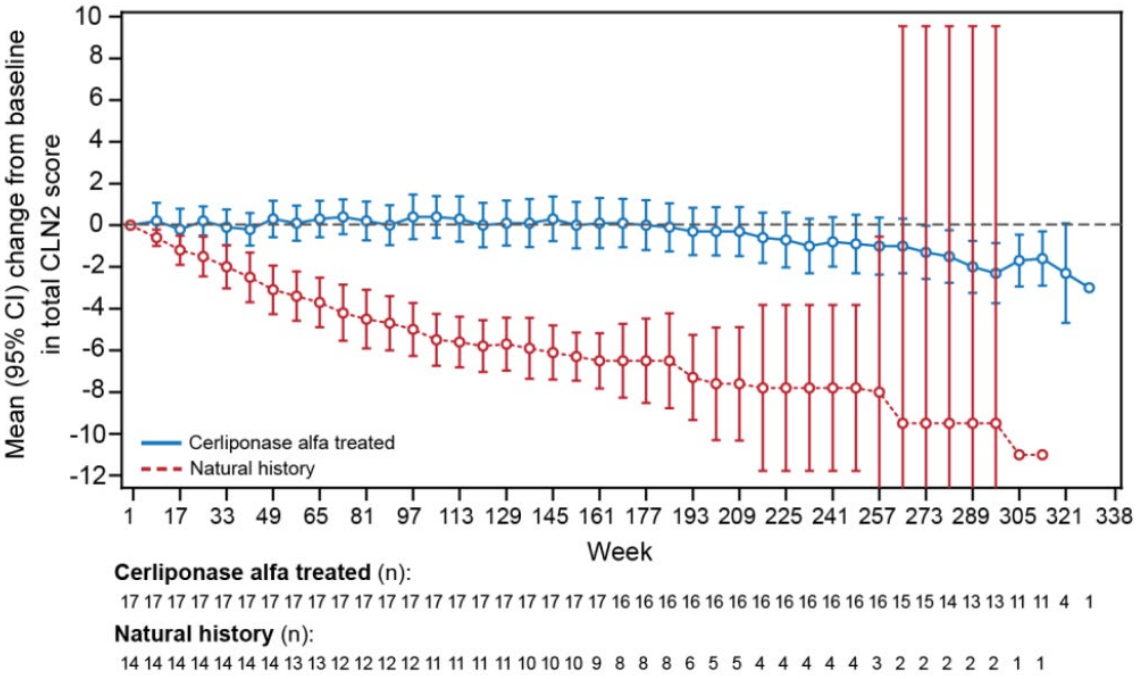

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**Figure 7: Change from baseline in CLN2 score by study week (1:1 matched NH and 190-201/202 population, 300 mg dosing period)**

**A**




**B**




Source: Schulz et al, 2024 (57).
A) ML score
B) MLVS score
Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; ITT, intent-to-treat; ML, motor language; NH, natural history.


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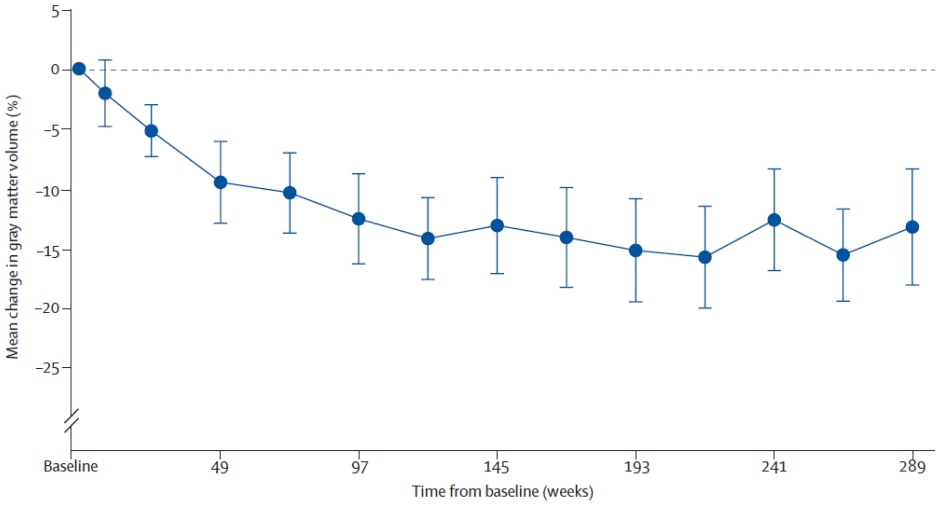
### B.2.6.2.5. Change from baseline on MRI measures

To analyse the impact of treatment on brain atrophy, MRI evaluation of brain volume and diffusion was performed. MRI volumetry was not assessed in the NH study, which precluded comparison of MRI data from treated participants with that from matched NH participants. Among treated participants, total grey matter volume declined over the duration of the study. Most of this decline occurred over the first 49 weeks of treatment, with a smaller incremental loss by Week 97, and little further change thereafter.

At the end of the parent study 190-201 (Week 49), the mean (SD) absolute change in whole brain volume was –4.4% (8.46) in the ITT population (57). At Week 97 in Study 190-201/202, there was a mean (SD) absolute change in whole brain volume of –3.9% (9.36). Change from baseline to last observation was –4.7 (10.54).

Moreover, the mean absolute change from baseline to Week 49 (end of the 190-201) was –9·7%. At Week 145, the change from baseline was –13·4% and, as of the last observation in the study, the change from baseline was –14·7%. This suggests that stabilisation in the loss of cortical grey matter volume occurs, but detection is delayed in relation to clinical scores (Figure 8) (57).

**Figure 8: MRI mean (±SD) percentage change in volume of grey matter analysis, 300 mg dosing period**




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients with available data at each timepoint | 23 | 22 | 23 | 23 | 23 | 23 | 21 | 23 | 21 | 19 | 19 | 19 | 17 | 15 |
| **Gray matter volume** | | | | | | | | | | | | | | |
| Mean (SD) volume, cm³ | 452·0 (87·7) | | 408·3 (88·5) | | 394·6 (89·3) | | 390·3 (84·3) | | 374·2 (89·9) | | 390·4 (78·4) | | 371·9 (54·6) | |
| Mean change from baseline | .. | | −10% | | −13% | | −13% | | −16% | | −13% | | −14% | |
| Annualised change from baseline | .. | | −11% | | −14% | | −15% | | −17% | | −14% | | −15% | |
| Annualised interval change | .. | | −11% | | −4% | | −1% | | −3% | | 2% | | 1% | |

Source: Schulz et al, 2024 .
Baseline is the last measurement before the first 300 mg infusion in 190-201. Values are the average of two readers
Abbreviations: MRI, magnetic resonance imaging; SD, standard deviation.


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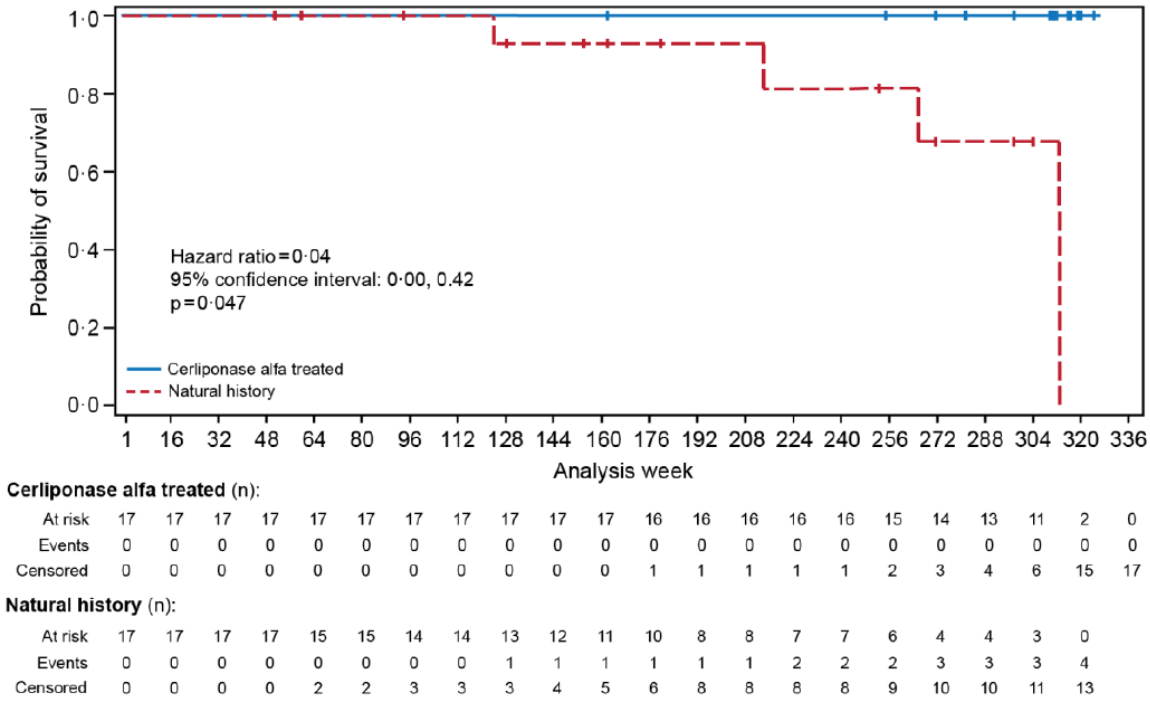
### B.2.6.2.6. Exploratory endpoints

Exploratory endpoints (OCT, VA, EEG, Denver II developmental screening test, PedsQL, CLN2 disease based QoL, and EQ-5D-5L questionnaire) are provided in Section B.2.6.5.

**Survival**

Figure 9 presents the survival from baseline analysis. This analysis demonstrated that treatment increases survival, with matched participants in 190-201/202 less likely to die than NH controls (HR: 0.04; 95% CI: 0.00, 0.42; p=0.047) (57). The median (IQR) time to death was 313 (266, 313) weeks in the NH cohort, and not reached in cerliponase alfa treated participants; during the full follow-up period, 0/17 treated participants died compared with 4/17 (24%) NH controls (44).

**Figure 9: Age of death using KM estimation, Cox Model (1:1 matched NH and 190-201/202 population)**




Source: Schulz et al, 2024 (57).
Survival is measured from birth to time of death (event) or time of last CLN2 assessment (censored). Cox model includes baseline ML score and baseline age as continuous covariates and genotype (common alleles) and sex as categorical covariates. Follow-up assessments up to the largest duration that is less than or equal to the full follow-up duration of the matched 201/202 subject are included for the matched analysis.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; KM, Kaplan-Meier; ML, motor language; NH, natural history.


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### B.2.6.3. Efficacy outcomes of Study 190-203

In total, the mean treatment duration for the ITT population in Study 190-203 was 272 weeks; all 23 participants had at least 162 weeks of cerliponase alfa treatment at the 300 mg dose (19). The mean (SD) length of time on study was 171.6 (7.12) weeks. The mean (SD) length of time on study drug was 140.4 (5.96) weeks. Administration of drug during the 24-week safety-follow-up period was not regarded as study drug.

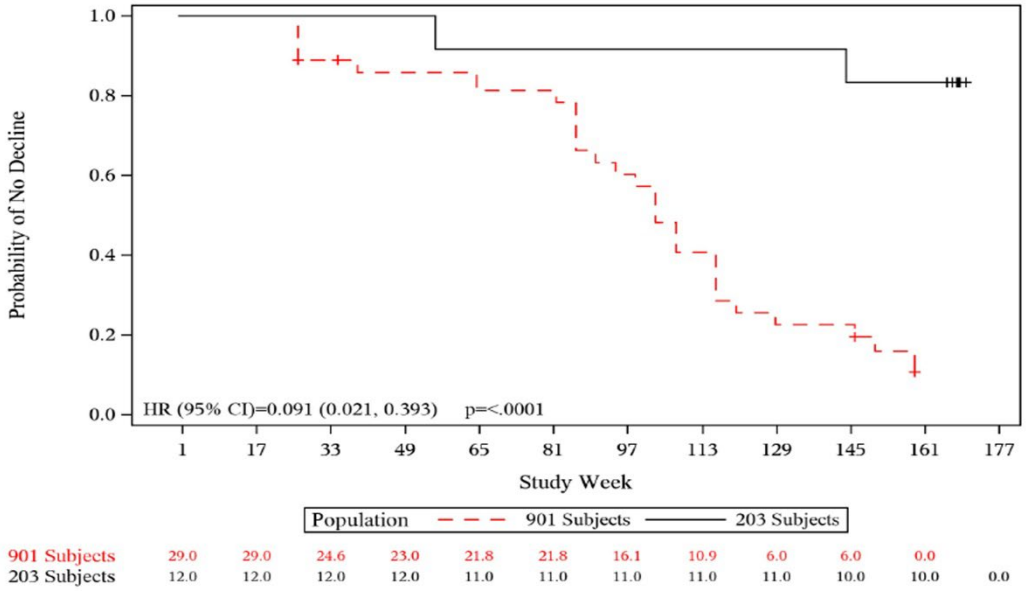
A total of 12 participants in Study 190-203 met criteria for matched analysis with NH participants (N=29). The 190-203 and NH groups were well balanced, with the slight exception of sex. In the NH evaluable population, 15.3 participants (52.8%) were female, and 13.7 participants (47.2%) were male.

#### B.2.6.3.1. Time to unreversed two-point decline or score of zero in ML score

A Cox proportional hazards model of time to unreversed two-point decline or score of zero in ML score demonstrated a statistically significant difference in matched 190-203 ITT participants as compared with matched NH controls (HR: 0.091; 95% CI: 0.021, 0.393; p<0.0001). The 190-203 participants were an estimated 91% less likely to experience an unreversed two-point decline or score of zero in ML score than matched NH participants (Figure 10). Two treated participants in the 190-203 ITT population had an unreversed two-point decline or score of zero post-baseline at Weeks 56 and 144. In contrast, 23.8 out of 29 NH participants (weighted according to inverse of number of matches) had an unreversed two-point decline or score of zero on the ML scale. The median time to event in NH controls was 103 weeks, and it was not reached in the treated population.


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**Figure 10: Time to first unreversed 2-point decline or score of 0 in ML (3:1 matched NH and 190-203 population)**




Source: Study 190-203 CSR, 2023 (19).
Note, an unreversed 2-point decline is any decline of 2 points or more that had not reversed to a 1-point decline (or better) at the last recorded observation. An unreversed score of 0 is a decline to 0 that had not increased to a score > 0 at last recorded observation.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; ML, motor language; NH, natural history.

Although CLN2 progression has a predictive nature, age may not be considered a proxy marker for CLN2 score, as a proportion of atypical patients (~13%), may develop CLN2 at a later age, and the age of patients with atypical CLN2 does not correlate well with their CLN2 score (10, 28). Therefore, age at treatment initiation is unlikely to be fully reflective of CLN2 score. Nevertheless, as Study 190-201/202 did not include children <3 years, Study 190-203 included an analysis of outcomes by age, including patient populations <2 years, <3 years, and ≥3 years, to verify cerliponase alfa efficacy in a population more representative of the UK patient population (Appendix O). A Cox proportional hazards model of time to unreversed 2-point decline or ML score of zero demonstrated a statistically significant difference in matched 190-203 ITT participants vs NH controls for participants <2 years (HR: 0.00; 95% CI: 0.00, NR; p<0.012), <3 years (HR: 0.00; 95% CI: 0.00, NR; p=0.0003), and ≥3 years (HR: 0.156; 95% CI: 0.019, 1.284; p=0.0488). Compared with untreated patients, cerliponase alfa treatment achieved significant attenuation of disease progression across all representative patient ages, with patients initiating treatment at a younger age exhibiting slower CLN2 disease progression.

#### B.2.6.3.2. Rate of decline in ML scale score

There was a statistically significant attenuation of the rate of decline on the ML scale for the matched 190-203 ITT participants compared with untreated NH controls, as demonstrated


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by a mean difference between groups (NH–203) of 1.15 points (SE 0.174); (95% CI: 0.80, 1.50 points; p<0.0001) (Table 28). The mean (SD) rate of decline in ML score was 1.30 (0.857) points per 48 weeks for matched NH controls (N=29) vs 0.15 (0.243) points in matched 190-203 ITT participants (N=12).

Additionally, the rate of decline per 48 weeks in the individual 0–3 point motor and language domains demonstrated that the significant cerliponase alfa treatment effects for motor and language endpoints were similar in magnitude (Table 28).

Results of the rate of decline in ML score based on age (<2, <3, and ≥3 years) were similar to results from the primary slope analysis (Appendix O).

**Table 28: ML scale – Rate of decline (3:1 matched NH and 190-203 population)**

| Rate of Decline | NH (N=29) | 190-203 (N=12) | Difference (NH–203) | p-value |
|---|---|---|---|---|
| **ML total score** | | | | |
| Mean (SD) | 1.30 (0.857) | 0.15 (0.243) | 1.15 | <0.0001 |
| SE | | | 0.174 | |
| Median | 1.28 | 0.00 | | |
| 25th, 75th percentile | 0.68, 1.77 | 0.00, 0.29 | | |
| Min, Max | 0.00, 3.73 | 0.00, 0.66 | | |
| 95% CI | 0.97, 1.62 | 0.00, 0.30 | 0.80, 1.50 | |
| **Motor score** | | | | |
| Mean (SD) | 0.59 (0.496) | 0.05 (0.120) | 0.54 | <0.0001 |
| SE | | | 0.098 | |
| 95% CI | | | 0.34, 0.74 | |
| **Language score** | | | | |
| Mean (SD) | 0.77 (0.715)† | 0.10 (0.146) | 0.67 | <0.0001 |
| SE | | | 0.145 | |
| 95% CI | | | 0.38, 0.97 | |

Source: Study 190-203 CSR, 2023 (19).
†N=28 for Study 190-901 language score matching.
The two-sample T-test with unequal variance was conducted at a significance level of 0.05.
Study 190-901 (NH) participants were weighted according to the number of matches: weights for 3, 2, and 1 Study 190-901 participant matched to a given Study 190-203 participant were 1/3,1/2, and 1 times N901/N203 respectively. N901 was the number of 190-901 participants matched to 190-203 participants (ie, 29) and N203 was the number of 190-203 participants who had matches (ie, 12). The 190-203 participants who had matches were assigned the weight of 1.
Rate of decline = (–1) x (48 x 7) x (ending score – starting score)/(ending date – starting date).
Abbreviations: CI, confidence interval; ITT, intent-to-treat; ML, motor language; NH, natural history; SD, standard deviation; SE, standard error.

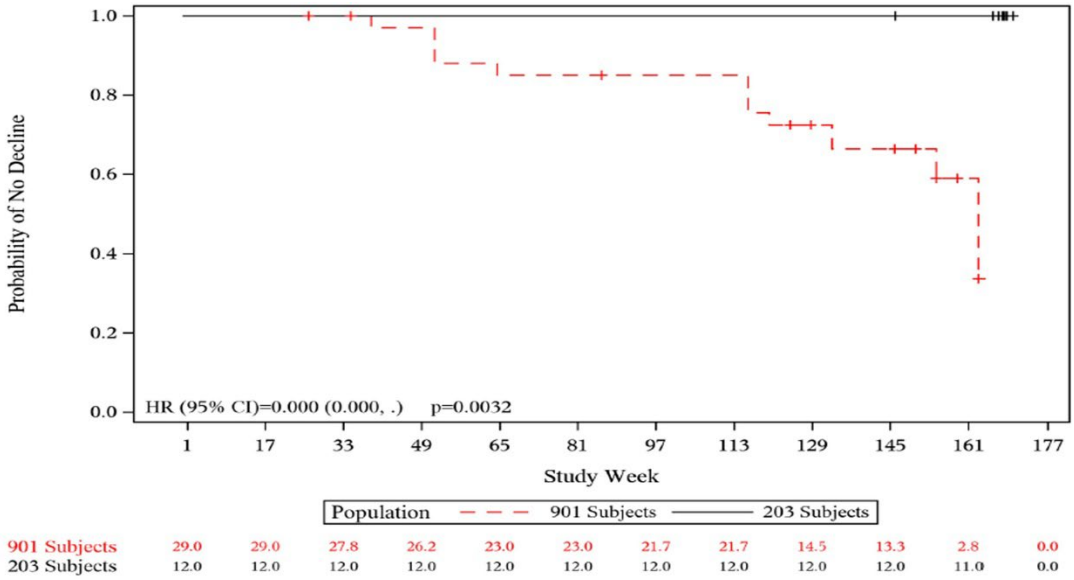
#### B.2.6.3.3. Time to ML score of zero

The event of unreversed ML score of zero is an event captured in longer term follow-up and represents the most severe/progressed state of the disease as captured by the ML scale:


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complete loss of independent ambulation and speech. 190-203 participants were significantly less likely than matched NH controls to have an unreversed decline to a score of zero in ML score (HR: 0.000; 95% CI, 0.0, NR; p=0.0032) (Figure 11). The median time until an ML score of zero was not reached among 190-203 ITT participants (i.e. no participant declined to ML=0) and was 163 weeks among NH controls.

**Figure 11: Time to score of 0 in ML score (3:1 matched NH and 190-203 population)**




Source: Study 190-203 CSR, 2023 (19)
An unreversed score of 0 is a decline to 0 that had not increased to a score > 0 at last recorded observation.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; ML, motor language.

#### B.2.6.3.4. Change in CLN2 Clinical Rating Scale score

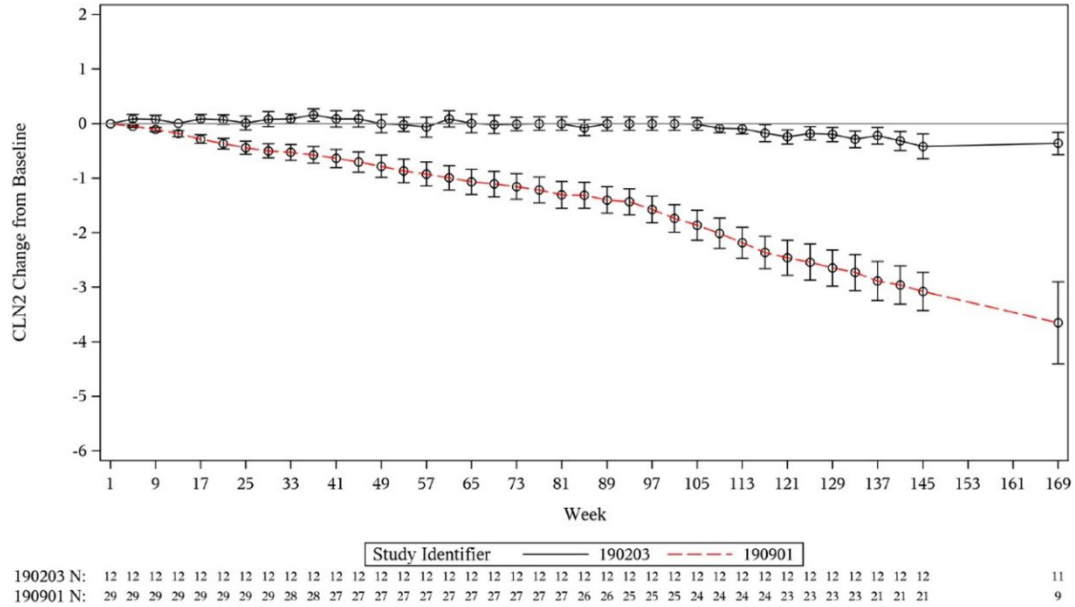
Mean (±SE) change from baseline in ML score by study week is displayed graphically in Figure 12A for 190-203 participants (N=12) matched NH controls (N=29). The observed trend for matched participants in 190-203 was stability of ML scores from baseline to end of study. There was a clear and sustained separation from matched NH controls post baseline. The matched NH participants declined in ML score at a faster rate than 190-203 participants, reflecting the natural progression of CLN2 disease.

Addition of the 0–3 point vision and seizure domains to the ML score provides a composite 0–12 point MLVS scale score that, when compared with the ML scale data, provides additional information about the contribution of vision and seizure functions to the overall treatment effect. Figure 12B shows absolute values and changes from baseline in the 0–12 point MLVS scale score for the matched 190-203 ITT population and NH controls. These results show that cerliponase alfa provides MLVS score stability, indicative of a durable and multidomain treatment effect relative to matched NH participants.

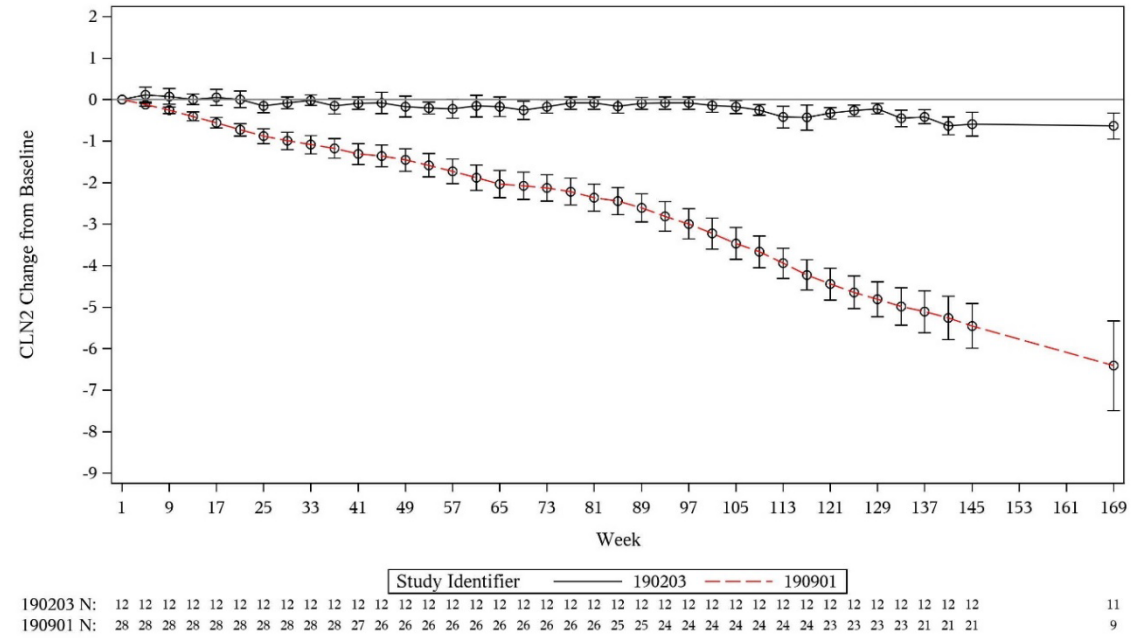

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**Figure 12: Change from baseline (±SE) in Hamburg CLN2 scores by study week (3:1 matched NH and 190-203 population)**

**A**




**B**



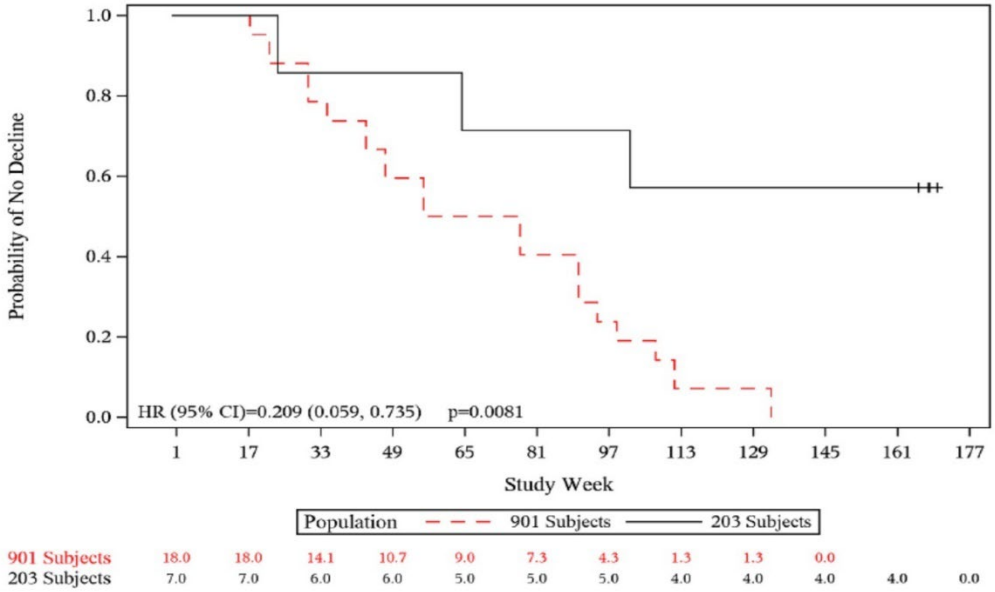

Source: Study 190-203 CSR, 2023 (19).
A) ML score; B) MLVS
Note: The 190-901 (NH) participants were weighted according to number of matches: weights for 3, 2, and 1 study 190-901 participant matched to a given study 190-203 participant were 1/3,1/2, and 1 times N901/N203 respectively. N901 was the number of 190-901 participants matched to 190-203 participants (i.e. 29) and N203 was the number of 190-203 participants who had matches (i.e. 12). The 190-203 participants who had matches were assigned the weight of 1.
Each participant in study 190-901 had their scores imputed to the time points using linear interpolation.
Baseline was defined as the last measurement prior to first infusion.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ITT, intent-to-treat; ML, motor language; MLVS, motor language vision seizure; NH, natural history; SE, standard error.


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#### B.2.6.3.5. Time to disease manifestation

Seven Study 190-203 participants had MLVS=12 at baseline. Figure 13 summarises the KM assessment of these seven participants' time to disease manifestation, matched to NH controls.

**Figure 13: KM of time of disease manifestation – Time to MLVS <12 for participants with baseline MLVS=12 (3:1 matched NH and 190-203 population)**




Source: Study 190-203 CSR, 2023 (15).
Disease manifestation was defined as post-baseline consecutive measurements of M, L, V, or S scores that were less than 3 and at least 22 days apart. The time of disease manifestation was defined as the time of the first of the 2 measurements demonstrating the deficit.
The 190-901 (NH) participants were weighted according to number of matches: weights for 3, 2, and 1 study 190-901 participant matched to a given study 190-203 participant were 1/3,1/2, and 1 times N901/N203, respectively. N901 was the number of 190-901 participants matched to 190-203 participants (i.e. 18) and N203 was the number of 203 participants who had matches (i.e. 7). The 190-203 participants who had matches were assigned the weight of 1.
Time of censor was related to the last record with MLVS=12.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan-Meier; L, Language; M, motor; NH, natural history;S, seizures; V, vision.

Treated participants were less likely to decline on the MLVS scale than their NH matches. The Cox proportional hazards model of time to disease manifestation demonstrated a 5-fold reduction in the likelihood of decline in comparison with NH controls (HR: 0.209; 95% CI: 0.059, 0.735; p=0.0081).

At Week 145, all 18 matched NH controls with baseline MLVS=12 had declined on the MLVS scale vs three of seven (43%) participants in 190-203. Median time to disease manifestation was 67 (95% CI: 34, 94) weeks in NH controls vs median not reached in 190-203 participants. The three participants in 190-203 with baseline MLVS=12 had their first


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decline (disease manifestation) at Weeks 25, 65, and 101. For two of the participants, disease manifestation was based on consecutive seizure domain scores of <3 points:

- Participant 1: baseline age=2.6 years; declined to a seizure score of 2 points (febrile seizure) at Week 101 when the participant was 4.5 years of age
- Participant 2: baseline age=2.5 years; decreased to a seizure score of 2 points at their Week 25 assessment when the participant was 3 years of age. Of note, this participant experienced their first seizure (an atonic seizure not captured in the CLN2 Clinical Rating Scale) only 1.2 months after starting cerliponase alfa
- Participant 3: baseline age=2.0 years; experienced a language domain score decline from 3 to 2 points at Week 65 when the participant was 3.2 years of age
- All 3 participants had an MLVS score of 12 points at last assessment.

In addition to time to disease manifestation based on the CLN2 Clinical Rating Scale score, medical history, full CLN2 Clinical Rating Scale (MLVS) scores, MRIs, and AEs were assessed to identify any signs and symptoms consistent with CLN2 disease onset in all seven pre-symptomatic participants identified by investigators. Based on medical history and AE presentation, one additional participant went on to manifest symptoms of CLN2 disease. This participant presented with symptoms that did not translate to a loss of function on the MLVS scale. Three of seven remained without any reported disease manifestation.

In total, 9 of 14 (64.2%) treated participants in Study 190-203 had no categorical decline in the MLVS score.

#### B.2.6.3.6. Change from baseline on MRI measures

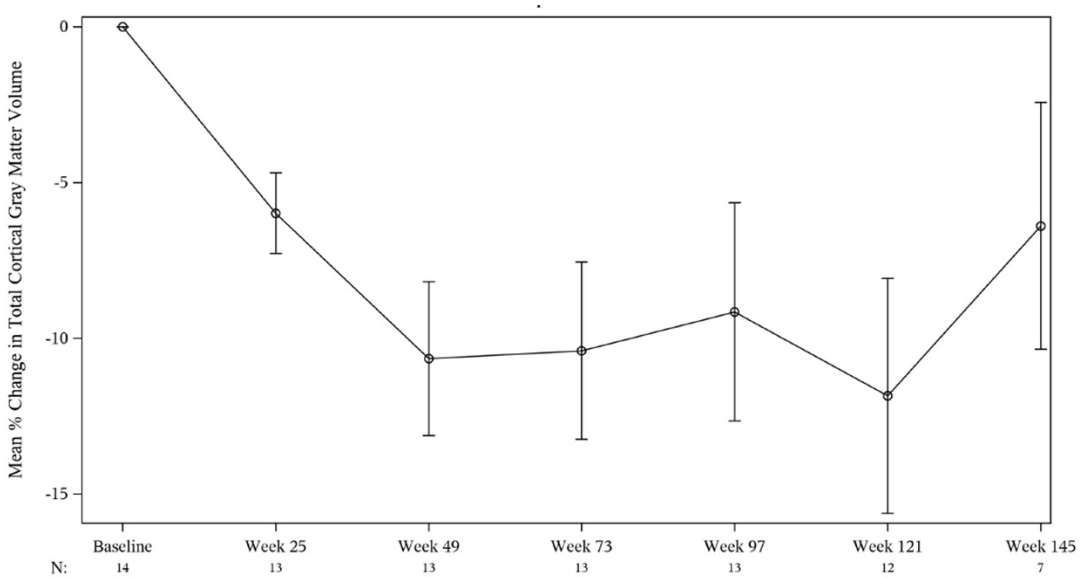
CLN2 disease is associated with cortical grey matter volume loss and related increase in proportion of cranial CSF. Cranial MRI was measured at screening, baseline, and every 24 weeks (±4 weeks) in Study 190-203 (N=14). Of note, 6 of 13 participants ongoing at Week 145 missed their MRI assessment; most MRIs were missed due to COVID-19 related hospital mandates.

At the last assessment (n=13), there was a mean (SD) percent change in total cortical grey matter of –10.3% (13.86) and mean (SD) change of –3.5 (2.48) as a percent of total brain volume, with a stable white matter and CSF volumes. There were small mean losses in cortical grey matter that occurred after treatment initiation, but these losses stabilised during the course of the study (Figure 14). Notably, total cortical grey matter volume changes in


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cerliponase alfa treated patients based on age, showed that volumes were stable in participants <2 and <3 years, with decreases in total grey matter volume stabilising after Week 49 through end of study in patients who initiated treatment ≥3 years (Appendix O).

**Figure 14: MRI mean (±SE) percentage change from baseline in volume of grey matter (190-203 ITT population)**




Source: Study 190-203 CSR, 2023 .
Baseline is defined as the last measurement prior to first infusion. Values are average of two readers.
Abbreviations: MRI, magnetic resonance imaging; SE, standard error.

### B.2.6.3.7. Exploratory endpoints

Exploratory endpoints (OCT, VS, EEG, mUBDS involuntary movement inventory, mUBDS seizure inventory, Denver II developmental screening test, PedsQL, CLN2 disease based QoL, and EQ-5D-5L questionnaire) are provided in Section B.2.6.5


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### B.2.6.4. Efficacy outcomes in the MAA cohort

The cerliponase alfa adherence rate of participants (FAS) during the MAA was 97%. Approximately 50% of the missed infusions were related to the COVID-19 pandemic.

None of the patients in the FAS achieved MAA stop criteria, and until the MAA data cut-off (September 2023), no patients stopped therapy for achieving their respective stop criteria.

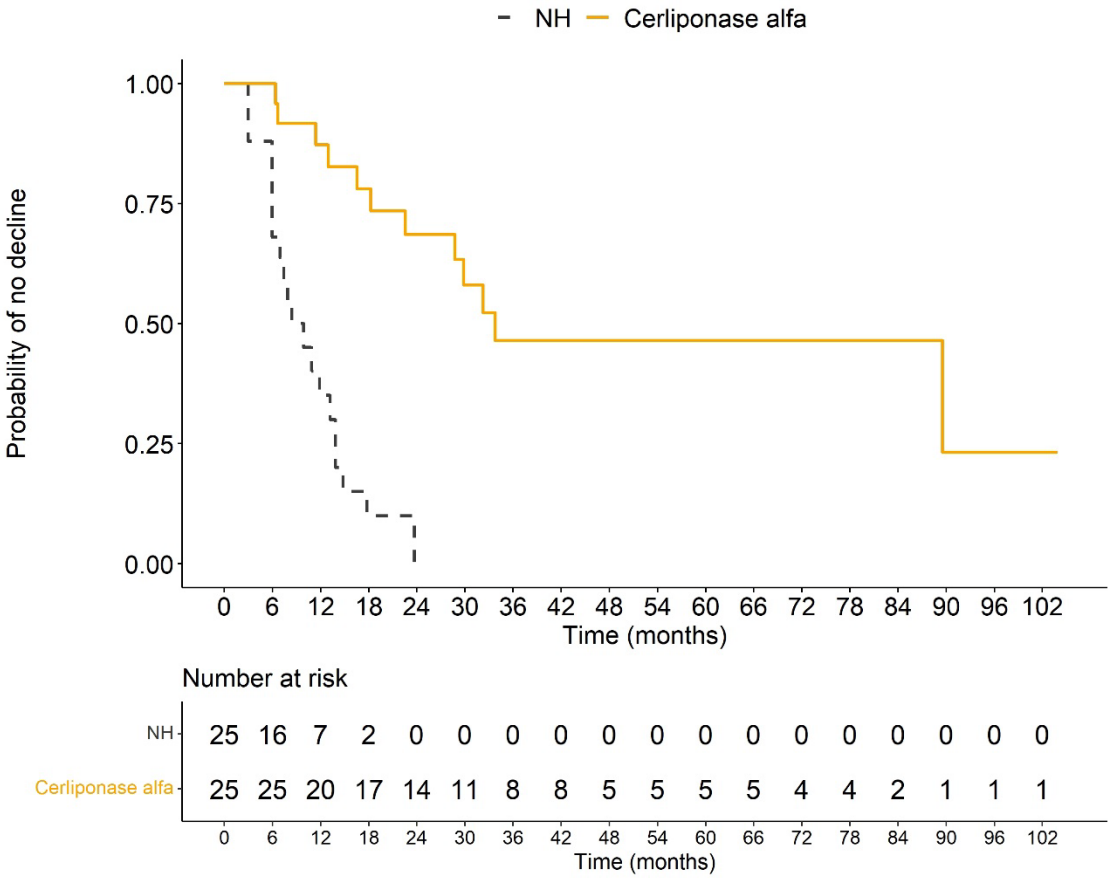
A total of 26 out of 35 participants in the MAA FAS met the criteria for matched analysis with NH participants (N=26). Of the MAA new starter cohort, a total of 17 out of 24 participants met the criteria for matched analysis with NH participants (N=17). The matched MAA FAS, new starter cohort, and NH populations were well balanced apart from sex, as this information was not collected for as part of the MAA.

#### B.2.6.4.1. Time to unreversed two-point decline or score of zero in ML score

A Cox proportional hazards model of time to unreversed two-point decline or score of zero in ML score demonstrated a statistically significant difference in the cerliponase alfa treated MAA FAS cohort, compared with matched NH controls (HR: 0.126; 95% CI: 0.05, 0.31; $p<0.0001$) (Figure 15). Treated patients were an estimated 87% less likely to experience an unreversed two-point decline or score of zero in ML score than matched NH participants. Median time to an unreversed two-point decline or score of zero was 32.87 months (95% CI: 21.94, NR) in the MAA FAS cohort, compared with 9.62 months (95% CI: 5.79, 12.82) in the matched NH control population.


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**Figure 15: Time to first unreversed 2-point decline or score of 0 in ML score (1:1 matched NH and MAA FAS population)**




Source: BioMarin MAA database, 2023 (11).
Note, an unreversed 2-point decline is any decline of 2 points or more that had not reversed to a 1-point decline (or better) at the last recorded observation. An unreversed score of 0 is a decline of 0 that had not increased to a score > 0 at last recorded observation. The Cox model includes baseline ML score and baseline age as continuous covariates.
Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; MAA, managed access agreement; ML, motor language; NH, natural history.

### B.2.6.4.2. Rate of decline in ML scale score

There was a statistically significant attenuation of the rate of decline on the ML scale for the matched MAA FAS participants vs untreated NH controls, as demonstrated by a mean difference between groups (NH–MAA FAS) of 1.33 points (SE 0.33); (95% CI: 0.67, 2.00 points; p=0.0002) (Table 29) (11). The mean (SD) rate of decline in ML score was 1.57 (1.53) points per 48 weeks for matched NH controls vs 0.23 (0.857) points in MAA FAS participants.


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**Table 29: ML scale – Rate of decline (1:1 matched NH and MAA FAS)**

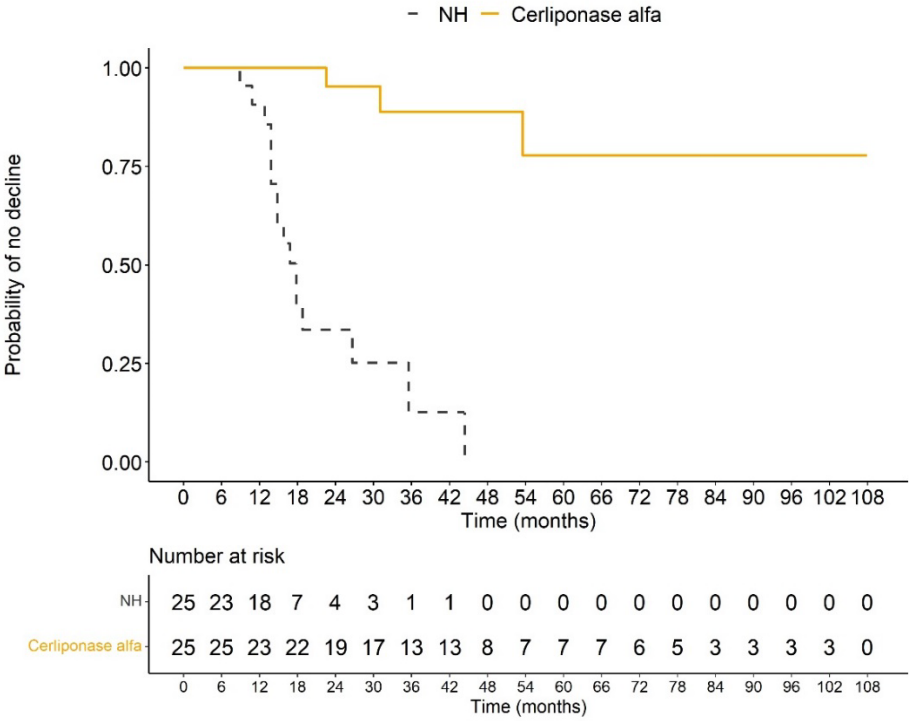
| Rate of Decline (Points/48 weeks) | NH | MAA FAS | Difference (NH–MAA) | Two-sided p-value |
|---|---|---|---|---|
| **ML total score** | | | | |
| n | 25 | 25 | | |
| Mean (SD) | 1.57 (1.53) | 0.23 (0.64) | 1.33 | 0.0002 |
| (SE) | | | 0.33 | |
| Median | 1.33 | 0.21 | | |
| 25th, 75th Percentile | 0.67, 2.07 | 0, 0.52 | | |
| Min, Max | 0, 7.38 | –1.77, 1.42 | | |
| 95% CI | 0.94, 2.20 | –0.03, 0.50 | 0.67, 2.00 | |

Source: BioMarin MAA database, 2023 (11).
Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; MAA, managed access agreement; ML, motor language; NH, natural history.

#### B.2.6.4.3. Time to ML score of zero

Cerliponase alfa treated MAA FAS participants were significantly less likely to have an unreversed decline or score of zero in ML score (HR: 0.023; 95% CI: 0.00, 0.12; p<0.0001) (Figure 16) (11). The median time until an ML score of zero was not reached in the matched MAA FAS cohort (i.e. no participant declined to ML=0), compared with 75 weeks (17.3 months; 95% CI: 13.5, 25.9) in the matched NH controls.

**Figure 16: Time to score of 0 in ML score (1:1 matched NH and MAA FAS)**




Source: BioMarin MAA database, 2023 (11).
Note, an unreversed score of 0 is a decline of 0 that had not increased to a score >0 at last recorded observation.
Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; MAA, managed access agreement; ML, motor language; NH, natural history.


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#### B.2.6.4.4. MRI

Although MRI assessments were completed, due to the nature of reports and a lack of consistency in assessing MRI results, no conclusions can be made. However, no unexpected outcomes were reported (11).

#### B.2.6.4.5. Neurological development

During the MAA evaluation period, neurological development was monitored in cerliponase alfa treated participants using the following tools: Bayley Scales of Infant Development III, Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV), Vineland Adaptive Behaviour Scale, and Wechsler Intelligence Scale for Children fifth edition (WISC-V). These tools are further described in Appendix R. Of note, was the inability to complete many of the assessments due to problems with neurodevelopment, age, and vision (11).

### B.2.6.5. Cerliponase alfa treatment effect on vision, seizures, mobility, and patient reported outcomes

This section presents the summarised relevant clinical effectiveness evidence for cerliponase alfa treatment effect on vision, seizures, movement, and PROs in participants with CLN2. These clinical areas of interest were defined in the decision problem and/or identified as areas of uncertainty in HST12. Detailed descriptions of each measure are included in Appendix R.

#### B.2.6.5.1. Cerliponase alfa treatment effect on vision

All clinical evidence points to continued deterioration of visual function in cerliponase alfa treated participants, with no significant indication that cerliponase alfa treatment could improve or stabilise vision loss (Appendix O) (19, 44, 46).

#### B.2.6.5.2. Cerliponase alfa treatment effect on seizures

**Descriptive analysis of seizures – frequency, severity, or type**

Study 190-801 Wave 1 (Appendix Q) evidence for seizure frequency suggests that overall seizure activity in cerliponase alfa treated participants was stable (46). Overall seizure activity in cerliponase alfa treated participants was primarily driven by primary generalised seizures and atonic seizures, both with a similar trajectory of an increase in the first year followed then by downward slope and an increase towards the fourth year of time on treatment. The observed trend for seizure frequency over time was not associated with any anti-epileptic medication change, or adjustments, as the medication change variable was seen to mirror the trajectory of primary generalised seizures. Although the overall seizure frequency was relatively stable across the observation period, the number of patient


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caregivers reporting that patient safety was a problem as a result of seizure activity was very low, and always below 35%. Additionally, the proportion of participants that required a doctor or hospital visit was very low across the observation period (46). Cerliponase alfa treated participants did not show increased severity of seizures, as evidenced through a reduction in the need for doctor/hospital visits (46), in addition to healthcare professionals' experiences (39).

### EEG

No clinically relevant changes or new safety concerns were identified upon the review of EEG data, across studies 190-201/202, 190-203, and the MAA new patient cohort. Compared with baseline, there were changes in epileptiform activity and frequency slowing, with a trend for increasing seizure activity observed, similar to that observed in Study 190-801 (Appendix Q).

**Table 30: Summary of cerliponase alfa treatment effect on EEG activity in participants with CLN2 disease across relevant clinical effectiveness evidence**

| Study (Ref) | EEG activity |
|---|---|
| 190-201/202 (44) | EEG evaluations from local and central vendor were analysed separately. 22/23 participants (96%) in the 190-201/202 ITT population had medical history of seizures and/or epilepsy. |
| 190-203 (19) | Seven participants (50%) showed new focal epileptiform activity, while five participants (36%) showed new generalised epileptiform activity and two participants (14%) showed both new focal and generalised activity. Eight participants (57%) showed new focal frequency slowing. Six participants (43%) showed new generalised frequency slowing, and one participant (7%) showed both new focal and generalised frequency slowing. |
| MAA – new patients (11) | Six participants reported epileptiform activity at baseline (n=13), with six participants reporting activity at 18 months (n=6), reducing to zero by the end of the evaluation period (n=3). EEG frequency slowing local vs generalised showed the same trend, with the number of participants remaining stable until 18 months of treatment, after which a decrease in the number of participants with activity was reported. |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; EEG, lectroencephalogram; ITT, intent-to-treat; MAA, managed access agreement.

### mUBDRS seizure inventory

The modified unified Batten Disease rating scale (mUBDRS) seizure inventory was used to assess seizure activity in Study 190-203 (19). There was a mean (SD) change of 0 (3.2) points from baseline to last assessment in mUBDRS seizure ratings. There were five participants who improved between 1 and 6 points, three participants who lost between 1 and 5 points, and six participants with no change from baseline. No change in or improvements in seizure score from baseline was observed in 78.5% (11/14) of cerliponase alfa treated participants, suggesting that the majority experienced stable seizure activity.

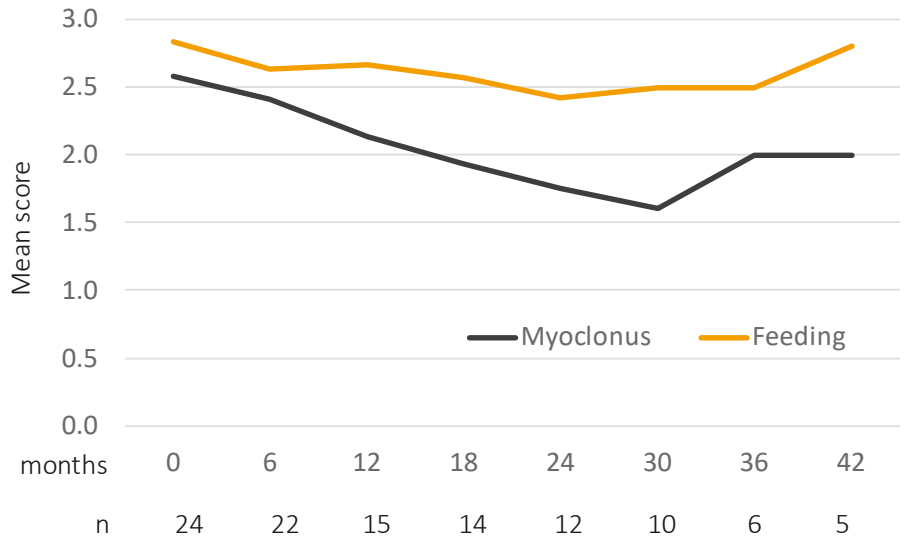

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### B.2.6.5.3. Cerliponase alfa treatment effect on movement disorders

#### Weill Cornell LINCL Scale

Weill Cornell LINCL Scale myoclonus and feeding/swallowing scores were collected every six months across the MAA evaluation period (71). Figure 17 presents the mean myoclonus and feeding scores for the new patient cohort. Scores remained relatively stable for both domains across the evaluation period.

**Figure 17: Weill Cornell LINCL Scale mean myoclonus and feeding domain scores over the MAA evaluation period (new patient cohort)**




Source: BioMarin MAA database, 2023 (11).
Abbreviation: MAA, managed access agreement.

#### mUBDRS involuntary movement inventory

The mUBDRS involuntary movement inventory was used to assess changes in movement in participants treated with cerliponase alfa during Study 190-203 (19). The majority (57%) of participants presented with no changed in mUBDRS involuntary movement score over the evaluation period. There was a mean (SD) change of –1.0 (2.4) points from baseline to last assessment. There was one participant who gained 2 points, five participants who lost between 1–5 points, and eight participants with no change in movement inventory score.

#### Descriptive analysis of onset and severity of movement disorders

Study 190-801 Wave 1 (Appendix Q) evidence for the effect of cerliponase alfa on movement disorders in participants with CLN2, indicated that the majority of participants treated with cerliponase alfa did not have any events or develop myocloni, and the majority of participants did not observe an increase in frequency or in severity of myocloni (Table 31) (46).


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**Table 31: Study 190-801 – Onset and severity of movement disorders**

| Myoclonus | Dystonia |
|---|---|
| • 66.7% did not experience a myoclonus event over the evaluation period**.** At a median time of 71 months, 33.3% did develop myoclonous<br>• 75% of participants did not experience an event of worsening in frequency over the evaluation period<br>• 25% of participants observed a sustained worsening in severity, and median time until sustained worsening was 69 months | • 21.1% participants remained without an event of dystonia at the end of the evaluation period<br>• Median time to onset was 19.4 months<br>• 17 out of 24 participants showed an increase in severity, with the median time to sustained worsening of 27.6 month |

Source: Study 190-801 Wave 1 presentation (46).

#### B.2.6.5.4. Cerliponase alfa treatment effect on patient reported outcomes

As no population-specific, clinically important difference estimates exist in the literature for the PedsQL, CLN2-QL, and EQ-5D-5L index scores in CLN2 disease, it was not possible to interpret the meaningfulness of the score changes during the cerliponase alfa effectiveness studies (Table 32). Furthermore, it was not possible to compare these results, as there are no longitudinal studies that have measured QoL in untreated participants with CLN2. However, directionality of results across all reported PRO outcomes and studies suggest consistency with the progression of disease.

**Table 32: Summary of cerliponase alfa treatment effect on PROs in CLN2 disease across relevant clinical effectiveness evidence**

| Study (Ref) | |
|---|---|
| **PedsQL™** | |
| 190-201/202 (44) | **PedsQL Parent Report for Toddlers**: Mean (SD) total score change from baseline was 2.6 (12.16) points at last observation in 190-201 (n=23), and mean (SD) change from baseline to study 190-202 completion was –15.0 (17.71) points (n=18)<br>**Peds QL Family Impact Module**: Mean (SD) total score change from baseline was 3.7 (19.04) points at last observation in 190-201 (n=23), and mean (SD) change from baseline to study 190-202 completion was –2.4 (15.69) points (n=20) |
| 190-203 (19) | No PedsQL summary data were reported.<br>Directionality of results suggests consistency with the progression of disease |
| MAA new patient cohort (11) | Mean (SD) score at baseline was 62.21 (17.78) (n=24), with a mean (SD) change from baseline of –2.22 (11.49) after 18 months (n=14), and change from baseline of 0.14 (11.75) after the 42 months of cerliponase alfa treatment (n=6) |
| **EQ-5D-5L‡** | |
| Study 190-201/202 (44) | Results suggest that there was no notable decline in either the domain or VAS scores |
| 190-203 (19) | No EQ-5D-5L summary data were reported.<br>Directionality of results suggests consistency with the progression of disease |


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| Study (Ref) | |
|---|---|
| MAA new patient cohort (11) | Mean (SD) score at baseline was 0.47 (0.30) (n=24), with a mean (SD) change from baseline of –0.03 (0.26) after 18 months (n=14), and change from baseline of 0.024 (0.22) after the 42 months of cerliponase alfa treatment (n=6) |
| **CLN2-QL** | |
| 190-201/202 (44) | Mean (SD) changes from baseline was 8.1 (14.33) points at last observation in 190-201 (n=22). In 190-202, mean (SD) change from baseline to study completion –0.6 (16.29) points (n=19) |
| 190-203 (19) | No CLN2-QL summary data were reported.<br>Directionality of results suggests consistency with the progression of disease |
| MAA new patient cohort (11) | Mean (SD) score at baseline was 78.19 (14.69) (n=24), with a mean (SD) change from baseline of 1.69 (8.67) after 18 months (n=14), and change from baseline of –2.87 (9.99) after the 42 months of cerliponase alfa treatment (n=6) |
| **Denver II developmental screening test** | |
| 190-201/202 (17) | At Study 190-201 completion, of the 22 participants (96%) evaluated, all 22 (100%) were classified as “suspect”. At Study 190-201/202 completion, 21 participants (91%) with a Denver II test at Week 97 were classified as “suspect”. Results indicate that development remained relatively stable over the evaluation period |
| 190-203 (19) | Each participant’s age equivalent score vs age of assessment for the 4 domains of the Denver II Development Scale indicate that the youngest participants developed at a normal rate, the oldest participants showed minimal to little development, and the mid age-range participants had slower development than normal<br>At baseline 64% participants were classified as “suspect”. At Study 190-203 completion 79% were classified as “suspect”, with 21% of participants moving from normal to suspect. Results indicate that development remained relatively stable over the evaluation period |
| **IT-QoL97** | |
| 190-203 (19) | No IT-QoL97 summary data were reported.<br>Directionality of results suggests consistency with the progression of disease |

†As no population-specific, clinically important difference estimates exist in the literature for the PedsQL, CLN2 disease based QoL, and EQ-5D-5L questionnaires in CLN2 disease, it was not possible to interpret the meaningfulness of the reported score changes; ‡Study 190-202 and Study 190-203 both had a protocol amendment that removed the EQ-5D-5L questionnaire to decrease study burden.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; IT-QoL97, 97-item full-length version; MAA, managed access agreement; ML, motor language; NH, natural history; PedsQL, Pediatric Quality of Life Inventory; PRO, patient reported outcome; SD, standard deviation; VAS, visual analogue scale.

### B.2.6.6. Summary

Since HST12, new data evaluating the clinical effectiveness of cerliponase alfa in CLN2 has become available across several studies, with over six years of cerliponase alfa treatment follow-up.

The primary efficacy endpoint (ML score) was assessed by several methods of analysis across all studies and compared cerliponase alfa treated patients with matched NH controls. This outcome is pivotal in establishing the magnitude of cerliponase alfa treatment effects on CLN2 disease progression and severity.


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Table 33 presents a primary outcome comparison across all the new clinical effectiveness evidence studies since HST12, with up to six years of follow-up. Firstly, 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, as compared with NH controls, with treated participants an estimated 87–94% less likely to experience an unreversed two-point decline or score of zero in ML score than matched NH controls.

Secondly, a statistically significant attenuation in rate of decline was observed for cerliponase alfa treated patients with CLN2 across all clinical effectiveness studies compared with matched NH controls, demonstrating the treatments' long-lasting CLN2 disease stabilisation.

Lastly, a significant increase in the time to unreversed ML score of zero was observed for all cerliponase alfa treated participants, who were an estimated 98–100% less likely to have an unreversed decline to a score of zero in ML score than untreated patients. This event, captured in longer term follow-up, represents the most severe/progressed state of the disease as captured by the ML score.

These results were comparable to the external RWE study DEM-CHILD-RX (Table 33; Appendix P). This retrospective observational study demonstrates the robustness of the cerliponase alfa clinical effectiveness evidence presented in this submission. Additionally, as DEM-CHILD-RX used a different NH matching criteria, this evidence further validates the indirect comparison with NH controls (190-901).

This comparison strongly demonstrates the significant beneficial impact of cerliponase alfa treatment for CLN2 disease.


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**Table 33: Evidence summary – Cerliponase alfa treatment effect on the adapted CLN2 ML Clinical Rating Scale compared with matched NH controls**

| | Study 190-201/202 | | | Study 190-203 | | | MAA FAS | | | DEM-CHILD-RX | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Time to first unreversed 2-point decline or score of 0 in ML score** | | | | | | | | | | | | |
| **Effect** | **HR estimate** | **95% CI** | **p-value** | **HR estimate** | **95% CI** | **p-value** | **HR estimate** | **95% CI** | **p-value** | **HR estimate** | **95% CI** | **p-value** |
| Treatment (cerliponase alfa vs NH) | 0.06 | 0.02, 0.25 | <0.0001 | 0.091 | 0.02, 0.39 | <0.0001 | 0.126 | 0.05, 0.31 | <0.0001 | 0.08 | 0.02, 0.28 | <0.0001 |
| **ML score – Rate of decline** | | | | | | | | | | | | |
| Difference NH – cerliponase alfa treated | 1.53 | | | 1.15 | | | 1.33 | | | 1.42 | | |
| 95% CI | 0.85, 2.21 | | | 0.80, 1.50 | | | 0.67, 2.00 | | | 0.74, 2.10 | | |
| p-value | <0.0001 | | | <0.0001 | | | 0.0002 | | | 0.0003 | | |
| **Time to ML score of 0** | | | | | | | | | | | | |
| **Effect** | **HR estimate** | **95% CI** | **p-value** | **HR estimate** | **95% CI** | **p-value** | **HR estimate** | **95% CI** | **p-value** | **HR estimate** | **95% CI** | **p-value** |
| Treatment (cerliponase alfa vs NH) | 0.00 | 0.00, 1.17 | 0.0088 | 0.00 | 0.0, NR | 0.0032 | 0.023 | 0.00, 0.12 | <0.0001 | 0.07 | 0.01, 0.40 | 0.0026 |

Sources: Final CSR for 190-202 (44); Study 190-203 CSR, 2023 (19); BioMarin MAA database, 2023 (11); DEM-CHILD-RX TLF, 2022 (73)
†Note that matching of NH controls to patients in studies 190-202 and 190-203 was based on equal ML score, age within 3 months, and genome with equal number of common alleles. Matching of NH controls to MAA cohorts was based on equal ML score and age within 3 months. Matching of NH controls to DEM-CHILD-RX patients was based on equal ML score and age within 12 months.
Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; HR, hazard ratio; MAA, managed access agreement; ML, motor language; NH, natural history.


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## B.2.7. Subgroup analysis

No analyses were undertaken to evaluate the treatment effect of cerliponase alfa in any sub-groups for Study 190-201/202, the MAA, DEM-CHILD-RX, or Study 190-801 based on stage of progression.

Study 190-203 included a subgroup analysis by MVLS score, presented in Section B.2.6.3.5. Of the patients with an MLVS score of 12 at baseline treated with cerliponase alfa, 43% had a decline in score at Week 145 vs 100% of NH controls (19). In total 64.2% of treated participants with MLVS score of 12 at baseline in Study 190-203 had no categorical decline in their MLVS score at the end of the study (19).

## B.2.8. Meta-analysis

Pairwise meta-analysis was not conducted.

## B.2.9. Indirect and mixed treatment comparisons

As Study 190-201/202, Study 190-203, MAA, DEM-CHILD-RX are open-label, non-comparative studies, the longitudinal NH study, Study 190-901, was considered the most relevant source of comparative data, allowing a comparison between clinical management including cerliponase alfa vs usual clinical management without cerliponase alfa. These data were re-analysed to focus on a population that matched the population enrolled in Study 190-201/202 and included as the main comparative analysis in Study 190-203, the MAA, and DEM-CHILD-RX. The matched analysis was performed to ensure a representative and relevant NH cohort/control for comparison.

### B.2.9.1. Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

## B.2.10. Adverse reactions

The safety and tolerability of cerliponase alfa was evaluated in Study 190-201/202, Study 190-203, and in three long-term safety studies: Studies 190-501, 190-502, and 190-504. An overview of these safety results is presented in Table 34. Full details are included in Appendix F. The results of the cerliponase alfa safety studies demonstrated that treatment at a dose of 300 mg administered every 14 days by ICV infusion was generally well tolerated and had an acceptable safety profile in paediatric participants with CLN2 disease. There was one participant across all studies that discontinued treatment due to an AE, no cases of AEs leading to dose reduction, and most AEs were mild or moderate in severity (Grade 1 or 2).


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**Table 34: Safety overview**

| Study (Ref) | 190-201/202 (44) | 190-203 (19) | 190-501 (47) | 190-502 (48) | 190-504 (49) |
|---|---|---|---|---|---|
| **AE category** | **(N=24), n (%)** | **(N=14), n (%)** | **(N=37), n (%)** | **(N=27), n (%)** | **(N=48), n (%)** |
| Any AE | 24 (100.0%) | 14 (100.0%) | 24 (64.9%) | 25 (92.6%) | 21 (43.8%) |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 | 0 |
| AEs leading to dose interruption | 15 (62.5%) | 5 (35.7%) | 5 (13.5%) | 1 (3.7%) | 9 (18.8%) |
| AEs leading to study drug discontinuation | 0 | 0 | 0 | 0 | 1 (2.1%) |
| Any SAE | 21 (88%) | 12 (85.7%) | 17 (45.9%) | 15 (55.6%) | 16 (33.0%) |
| SAEs leading to dose reduction | 12 (50%) | 0 | 0 | 0 | 0 |
| SAEs leading to dose interruption | NR | 2 (14.3%) | 4 (10.8%) | 0 | 7 (14.6%) |
| SAEs leading to study drug discontinuation | 0 | 0 | 0 | 0 | 1 (2.1%) |
| Any AE CTCAE Grade ≥3[†] | 21 (87.5%) | 10 (71.4%) | 14 (37.8%) | 8 (29.6%) | 12 (25.0%) |
| Death | 0 | 0 | 1 (2.7%) | 0 | 1 (2.1%) |
| Any treatment-related AE | 23 (96%) | 11 (78.6%) | 11 (29.7%) | 16 (59.3%) | 6 (12.5%) |
| Treatment-related SAEs | 8 (33%) | 7 (50.0%) | 2 (5.4%) | 6 (22.2%) | 1 (2.1%) |
| AESI[‡] | | | | | |
| Status epilepticus | 2 (8.3%) | 1 (7.1%) | 1 (2.7%) | 4 (14.8%) | 2 (4.2%) |
| Hydrocephalus | 0 | 0 | 0 | 0 | 0 |
| Meningitis | 0 | 0 | 1 (2.7%) | 0 | 3 (6.3) |
| Hypersensitivity | 18 (75.0%) | 10 (71.4%) | 0 | 7 (25.9%) | 4 (8.3%) |
| TREs | 24 (100.0%) | 14 (100.0%) | 15 (40.5%) | 19 (70.4%) | 14 (29.2%) |
| Device-related events | 20 (83.0%) | 5 (37.5%) | 19 (51.4%) | 3 (11.1%) | 10 (20.8%) |
| Cardiovascular events | 7 (29.0%) | 3 (21.4%) | 0 | 3 (11.1%) | 0 |
| Unexpected rapid decline in CLN2 score | 0 | 0 | NR | 2 (7.4%) | NR |

Percentages were calculated using the total number of participants in the safety population (N for each treatment group) as the denominator. Participants with more than one AE of the same category were counted only once for that category.
†Relationship to the study drug and CTCAE grade was assessed by the investigator; ‡Prospective selection of AESI was based on non-clinical findings, known effects of other enzyme replacement therapies, and literature review of AEs associated with ICV delivery systems.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CLN2, neuronal ceroid lipofuscinosis type 2; CTCAE, common terminology criteria for adverse events; ECG, electrocardiogram; SAE, serious adverse event; TRE, temporally-related events.


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### B.2.10.1. Mortality

No deaths were reported during studies 190-201/202, 190-203, and 190-502. Further, Study 190-202 included a dedicated survival/time to death analysis of cerliponase alfa treated patients vs NH controls (Section B.2.6.2.6). This analysis demonstrated that treated participants were significantly less likely to die than matched NH controls (HR: 0.00; 95% CI: 0.00, NR; p=0.0008) (57).

One death was reported in Study 190-504. This patient experienced a treatment-refractory dystonic event which was assessed by the investigator as unrelated to the drug or the ICV device (49). [redacted]

One death was recorded in a nine-year-old female participant, during Study 190-501 (47). The investigator confirmed the reason for the participant's progression of CLN2 disease was due to the family's decision to stop treatment with cerliponase alfa and begin palliative care. The causality of event disease progression was assessed as not related to cerliponase alfa by the investigator and BioMarin.

### B.2.10.2. AE summary

#### B.2.10.2.1. Common AEs

The most common cerliponase alfa treatment related AEs across all five studies were pyrexia, hypersensitivity, and vomiting, and are known adverse drug reactions (ADRs) in the product labelling (24) and most were assessed as Grade 1 or 2 in severity (Appendix F).

Grade 3 AEs were relatively common with more than half of trial participants experiencing at least one event in studies 190-201/202, and 190-203. Specifically, 75% of participants in Study 190-201/202, and 71% in Study 190-203 experienced at least one Grade 3 AE event, although the majority of these were not related to cerliponase alfa, with only 4/18, and 3/10 AEs reported as treatment related, respectively. The number of Grade ≥3 AEs reported in the long-term safety studies were lower, ranging from 25–38%.

#### B.2.10.2.2. Cardiovascular AEs

Patients with lysosomal storage disorders, including other forms of NCL such as CLN3, can experience cardiac abnormalities (75). However, cardiac complications have only been


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described in one atypical case of CLN2, for an individual who developed ventricular tachycardia and an atrioventricular block at 23 years (76). The long-term effects of cerliponase treatment and cardiac abnormalities were therefore examined across the evidence base for CLN2. Based on the cumulative data review of cardiac AEs and ECG events, there is no evidence of any cardiac structural or rhythm abnormalities identified in any safety trials or in the expanded access program, therefore no new safety concerns were identified. ECG assessments were also carried out during the MAA evaluation period, with a low number of clinically significant ECG-12 abnormalities reported (Appendix R).

#### B.2.10.2.3. Device-related AEs

Device-related AEs were also commonly reported across all safety studies, with the highest incidence reported in Study 190-201/202 (88%) (57). The majority of device related AEs were caused by device-related infections, and BioMarin has upgraded all these device-related infections to SAEs in BioMarin's safety database (seriousness criteria: medically significant). All of the events of device-related infection were assessed as related to the ICV device and not related to cerliponase alfa treatment and the ICV device was successfully replaced without complication and without discontinuation of study drug in all cases. BioMarin have taken steps to develop educational materials for healthcare professionals, describing the correct infusion preparation, the ICV drug administration and the monitoring of the patients, to reduce the risk of these infections. Notably, during an advisory board held with healthcare professionals in November 2023, advisers agreed that the rate of ICV infusions that lead to infection would be significantly lower in real-world clinical practice vs that reported in 190-201/202 and 190-203 (42). During the clinical trial program, infusions were administered by clinicians; however, since HST12, cerliponase alfa is administered by nurses in the clinical setting, and there has been a substantial reduction in infection rates. One adviser stated that currently they experience fewer than 1 in 700–1000 infusions resulting in an infection (42).

#### B.2.10.2.4. Seizures and epilepsy

Seizures and epilepsy were among the most common AEs across all studies (Table 34; Appendix F). During all studies, convulsion AEs were managed medically, and did not lead to withdrawal from the study. It is not clear whether these convulsion AEs are treatment related or an indication of worsening or uncontrolled symptoms of the underlying disease. Besides being related to the underlying disease, seizures could potentially also be caused by the ICV device, ICV drug administration, or protein administration. As seizures are a common manifestation of CLN2 disease, with almost all patients reporting seizures at study baseline, convulsion AEs (seizure and epilepsy) are expected to occur in this patient


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population making the interpretation of these results limited. An overview of seizure severity and frequency in cerliponase alfa treated patients with CLN2 is included in Section B.2.6.5.

### B.2.10.3. Safety summary

The reported AEs were consistent with the known safety profile of cerliponase alfa, the participants' underlying disease or concurrent conditions, and side effects of concomitant medications. Considering the benefit-risk profile of cerliponase alfa in CLN2 disease, no significant safety concerns were identified for administration of cerliponase alfa across all presented studies.

## B.2.11. Ongoing studies

There are currently four ongoing trials investigating cerliponase alfa for CLN2. These are summarised in Table 35.

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**Table 35: Summary of ongoing studies**

| Study name (Ref) | Study end date | Study description |
|---|---|---|
| **190-801** (77) | 2027 | **A retrospective analysis of the DEM-CHILD Registry**<br>The primary aim of this study is to evaluate clinical outcomes in CLN2 patients treated with cerliponase alfa using data captured from time of enrolment in the DEM-CHILD registry through all available data at time of analysis<br>The long-term effectiveness of cerliponase alfa in patients with CLN2, in addition to changes in disease progression and symptomatology of CLN2 disease will be assessed. Specific study objectives will be covered in three planned analysis waves over an approximate 5-year project period (February 2023 through Q3 2027) to explore different clinical outcomes and different patient populations treated with cerliponase alfa.<br>Comparison between the DEM-CHILD treated cohort and a NH cohort of untreated patients captured in DEM-CHILD prior to availability of cerliponase alfa may be performed when the clinical outcomes are also available for untreated patients. |
| **190-501** (47) | 2030 | **Multicentre, post-marketing, observational, long-term safety study in the USA**<br>Interim results for Study 190-501 (Appendix F) were provided by the sixth annual report covering the period from 10 March 2022 to 09 March 2023. Progress updates are reported annually. This study is in the third year of recruitment and is ongoing. Recruitment is expected to continue until August 2023. Thereafter, a 7-year follow up period ensues, with last participant out expected in August 2030.<br>The primary objective of the study is to evaluate the long-term safety of cerliponase alfa in participants with CLN2 disease.<br>The secondary objectives are as follows: (i) To further assess the occurrence of serious hypersensitivity reactions (including anaphylaxis), serious cardiovascular AEs, and serious device-related complications; (ii) To evaluate the effects of Grade 3 or higher SAEs on participant performance on the CLN2 Clinical Rating Scale (ML domain) |
| **190-504** (49) | 2029 | **Observational non-interventional post-authorisation safety study**<br>Interim results for Study 190-504 (Appendix F) were provided by the sixth annual report covering the period from 27 April 2022 to 26 April 2023. Progress updates are reported annually. Recruitment into the study began on 10 October 2019 and is currently ongoing. The study duration is up to 10 years. Participants will be enrolled in the study over a period of at least 8 years from the 10 October 2019. Data on individual participants will continue to be collected for at least 2 years from the time the last participant is enrolled or until the study is completed.<br>The primary objective of this study is to evaluate the long-term safety of cerliponase alfa in patients with CLN2 disease.<br>The secondary objectives of this study include the following: (i) To further assess the occurrence of serious hypersensitivity reactions (including anaphylaxis), serious cardiovascular AEs, and serious device-related complications; (ii) To evaluate the effects of Grade 3 SAEs on patient performance on the CLN2 Clinical Rating Scale (ML domains) |
| **190-506** (78) | 2029 | **Cerliponase alfa observational survey to evaluate long-term safety of cerliponase alfa in patients with CLN2 in Japan**<br>An observational survey for patients in Japan with a confirmed diagnosis CLN2 disease, who intend to/are currently being treated with cerliponase alfa.<br>The registered population will consist of all CLN2 patients in Japan who are being treated with cerliponase alfa. Patients will be registered over a period of 9 years from the date of product launch in Japan (06 January 2020).This study is currently recruiting.<br>The primary objective is to evaluate the long-term safety of cerliponase alfa in patients with CLN2 disease.<br>Secondary objectives include the following: to further assess the occurrence of serious hypersensitivity reactions (including anaphylaxis), serious cardiovascular AEs, serious device-related complications and to evaluate the effects of Grade ≥3 SAEs, on patient performance on the CLN2 Clinical Rating Scale (ML domains). |

Abbreviations: AE, adverse event; CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; Q3, quarter 3; SAE, serious adverse event.


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## B.2.12. Interpretation of clinical effectiveness and safety evidence

The additional clinical evidence base for cerliponase alfa for the treatment of CLN2, collected since HST12, consists of the completed studies 190-201/202, 190-203, the MAA cohort, in addition to DEM-CHILD-RX, and interim Wave 1 evidence from Study 190-801. Furthermore, three long-term cerliponase alfa safety studies with additional data have been reported; studies 190-501, 190-502, and 190-504. This additional evidence has comprehensively addressed key areas of uncertainty highlighted in the MAA (14).

### B.2.12.1. Long-term CLN2 disease stabilisation

Evidence since HST12 demonstrates long-term disease stabilisation is provided by cerliponase alfa treatment in patients with CLN2. As presented in Section B.2.6.6 (Table 33), treatment with 300 mg cerliponase alfa every other week for at least 96 weeks was shown to result in preservation of motor and language function. Clinically meaningful and statistically significant slowing of disease progression was maintained across all clinical effectiveness studies, including expected but manageable safety events, with up to six years of cerliponase alfa treatment follow-up.

Each of the effectiveness studies provides unique additional information on cerliponase alfa treatment effect on CLN2 disease compared with data presented in HST12; (i) Study 201/202 was completed with the longest follow-up for cerliponase alfa treated patients; (ii) Study 190-203 captured data in younger patients (<3 years) in addition to patients with higher ML baseline score starting distributions compared with Study 190-201/202; (iii) the MAA represents a UK based RWE cohort; and (iv) DEM-CHILD-RX provides an external RWE comparison, validating the NH matched outcomes across the other effectiveness studies.

The dedicated survival/time to death analysis of cerliponase alfa treated patients vs NH controls in 190-201/202 demonstrated that cerliponase alfa treated patients were significantly less likely to die. Median age of death for NH controls was 10.4 years and none of the cerliponase treated participants died during the study (mean age at last dose 10 years). In CLN2 disease, symptomatic SoC (e.g., mechanical ventilation and gastrostomy tube feeding) can prolong life, but such measures do not generally alter disease progression and thus prolongation of life might be predominantly in the most progressed stages of disease. The supportive analyses of the significant delay in time to reach a score of zero in ML score in the cerliponase alfa treated participants across all the presented clinical effectiveness studies, therefore suggests that the increased survival in treated patients is accompanied by significant preservation of function.


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The ML score itself has inherent limitations in that it does not capture all aspects of CLN2 disease and, moreover, lacks granularity, with domain scores covering a comparatively wide range of abilities. However, the score was selected as the primary efficacy outcome in the clinical effectiveness studies as it provided an objective assessment that could be used to compare outcomes in treated patients with those of historical controls. Furthermore, the ML score stabilisation observed across the presented evidence base was consistent with the experiences described by both healthcare professionals and patient advocates during two separate advisory boards held in July 2023 (13, 39). Firstly, six England-based healthcare professionals with experience of treating patients with CLN2, and the Chair of the BDFA, all agreed that the trajectory of a patient's ML score for the majority of patients with CLN2 is dependent on their score at baseline. Patient advocates, including three parent representatives, verified that children with CLN2 diagnosed earlier in the pathway, who are treated with cerliponase alfa, had better outcomes. This is consistent with the improved outcomes seen in cohorts which included younger participants such as 190-203. It is well established that for this pathophysiology of lysosomal storage disorders, where storage material accumulates over time, an early diagnosis and treatment before the onset of irreversible pathology is primordial (79).

Patient advocates stressed that the difference in outcomes between siblings in families with two children with CLN2, diagnosed at different times in the disease pathway, inferred how transformative treatment with cerliponase alfa has been. In families with two affected children, the younger sibling who started cerliponase alfa treatment earlier in life and with a higher ML score was almost completely healthy (13). Advocates noted that QoL had improved, due to the increased time that cerliponase alfa has allowed them to spend as a family, and that they had a better outlook on life as a result (13).

The long-term and significant slowing of CLN2 disease progression was observed across the presented evidence base highlights the substantial benefit of cerliponase alfa in attenuating CLN2 disease progression.

#### B.2.12.2. Higher ML score starting distribution

Whilst robust real-world evidence for earlier CLN2 diagnosis has not been reported since HST12, during the July 2023 healthcare professional advisory board, advisers noted that they have observed slight improvements in ML starting distributions in the clinic (39). Additionally, during a follow-up advisory board in November 2023, one clinician stated that they were definitely seeing an increasing number of patients diagnosed with higher ML scores (42). Advisers also mentioned that the MAA starting distribution may have been affected as a result of the COVID-19 pandemic (39). The COVID-19 pandemic was


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anticipated to be a factor that may still be affecting new UK CLN2 patient baseline scores, with some children potentially yet to be diagnosed as a direct impact of pandemic related clinical delays. The full fallout of the pandemic is therefore still to be seen, a pattern that has also been observed for other conditions in the GOSH clinic (39). The total level of improvement in ML starting distribution since HST12 may consequently not be fully realised as a result of the pandemic.

Furthermore, data collection for patients who started treatment after the approval of the MAA, may be skewed by patients who were already awaiting therapy, particularly in the first years of the MAA evaluation period. Those patients awaiting therapy were progressed in clinical terms, but not enough to not start therapy, which may affect the interpretation of the data from the MAA.

Nevertheless, progress has been made to improve CLN2 diagnosis across the UK, with the goal of therefore improving baseline ML scores. As outlined in Section B1, the pivotal development is that the Newborn Genomes Programme Generation Study has included *CLN2*/*TPP1* in its list of genes, which may pave the way for the majority of CLN2 diagnoses to be achieved before disease progression (43).

The impact of initiating cerliponase alfa in participants in earlier stages of disease progression, i.e. patients with higher CLN2 Clinical Rating score starting distributions, was evidenced in Study 190-203, during which seven pre-symptomatic participants (50%) who had ML scores of 6 points and MLVS scores of 12 points at baseline were assessed. An analysis of time to disease manifestation in these participants demonstrated that treated participants were less likely to decline on the MLVS scale than their NH matches, with a 5-fold reduction in the likelihood of consecutive motor, language, vision, and seizure function deterioration (HR: 0.209; 95% CI: 0.059, 0.735; p=0.0081). At Week 145, 100% of the pre-symptomatic at baseline NH participants had declined vs 43% of cerliponase alfa treated participants, and median time to disease manifestation was 67 weeks vs not reached in untreated vs treated participants, respectively. Evidence of cerliponase alfa efficacy was also demonstrated in aggregate scores using seizure and vision subscales (MLV and MLVS), in which there was marked attenuation of CLN2 disease progression compared with NH controls. These analyses therefore indicated the durable effect of cerliponase alfa on vision and seizure function as well as ML.

Furthermore, total cortical grey matter volume changes in cerliponase alfa treated patients based on age, showed that whilst an initial loss of cortical grey matter followed by stabilisation was reported in participants ≥3 years, volumes were stable in treated


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participants <2 and <3 years (Appendix O). Although interpretation of these findings is limited by the absence of comparator data for NH controls, Loebel et al, have shown progressive loss of supratentorial cortical grey matter (up to 12·5 % per year) in a longitudinal cohort of untreated patients with CLN2 disease (80). These findings therefore indicate that the earlier cerliponase alfa treatment is initiated, the more likely brain atrophy and CLN2 disease progression may be prevented.

#### B.2.12.3. Impact of cerliponase alfa on vision, seizures, and movement disorders

Whilst the impact of cerliponase alfa treatment on vision, seizures, and mobility in participants with CLN2 disease is captured via the validated CLN2 Clinical Rating scale, supportive evidence was also collected via additional assessments in the relevant effectiveness studies.

There was no significant indication that cerliponase alfa treatment could improve or stabilise vision loss using specialised ophthalmological endpoints carried out in Study 190-201/202, Study 190-203, and the MAA. Patients with CLN2 disease have progressive loss of vision and are typically blind by the age of 7–10 years (57). ICV administration of cerliponase alfa is not expected to have an effect on the retina, and decline in vision accompanied by progressive retinal degradation has been documented in patients receiving treatment (81). Consistent with this finding, outcomes of visual assessments across the presented evidence base did not indicate cerliponase alfa associated improvements in vision. Additionally, scores on the vision domain of the CLN2 Clinical Rating Scale declined in both treated and NH controls, although the decline was somewhat delayed in treated patients, suggesting that despite the absence of an effect on retinal degradation, there might be an effect on the occipital visual cortex. Studies in canine models of CLN2 disease have shown that intravitreal (IVT) injections of cerliponase alfa can preserve retinal structure and function, and clinical trials evaluating the safety and efficacy of IVT cerliponase alfa are ongoing (3, 82, 83). Eight patients receiving ICV cerliponase alfa under the MAA received additional IVT administration of cerliponase alfa to a single eye every two months at GOSH over a 2.5-year period (2021–2023) as part of independent (ex-BioMarin) research. The results of this research have been published (84). Outcomes relating to this research were not collected under the MAA (11).

No clinically relevant changes or new safety concerns were identified upon the review of seizure data across the evidence base. Evidence for seizure frequency suggested that overall seizure activity in cerliponase alfa treated participants was stable, an effect that was not associated with any changes in medication (46). Additionally, the severity of seizures


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was improved via cerliponase alfa treatment, as evidenced through a reduction in the need for doctor/hospital visits recorded in Study 190-801 (Appendix Q) (46). The July 2023 advisory board with healthcare professionals experienced in treating patients with CLN2, supported these observed seizure outcomes (39). Advisors emphasised that seizures had been easier to manage in cerliponase alfa treated patients with CLN2, since the 2017 positive recommendation and the routine availability of cerliponase alfa treatment (39). Seizures were reported as less frequent, and less severe in patients receiving cerliponase alfa. Advisers also noted that in the past, a patient with CLN2 may have required hospitalisation for seizures, however this was less likely on cerliponase alfa treatment. As described in B.1.3.4.2, patient advocates emphasised that seizure severity had a large impact on the QoL of patients and their families (13).

Further, studies examining patient movement disorders indicated that most cerliponase alfa treated patients did not experience increases in frequency or severity of involuntary movements. During Study 190-203, 57% of patients presented with no changed in mUBDRS involuntary movement score over the evaluation period (19). Furthermore, the majority of cerliponase alfa treated participants in Study 190-801 (Appendix Q) did not experience worsening of myoclonus-related symptoms; 66.7% did not experience a myoclonus event, and 75% of patients did not observe increases in either frequency or severity of myoclonus-related symptoms (46). This is likely to have significant implications for patient QoL, with one clinical expert stating that myoclonus is very painful and difficult to treat (14).

#### B.2.12.4. Patient reported outcomes – cerliponase alfa and quality of life

The clinical effectiveness findings were supported by the exploratory outcomes (evaluated via the PedsQL™ Module for Pediatric Quality of life Inventory, the Denver II developmental screening test, the CLN2 disease based QoL instrument, EQ-5D-5L, and IT-QoL97) to explore the impact of treatment on age-appropriate developmental milestones and QoL. Although it was not possible to evaluate the clinical meaningfulness of score changes across studies 190-201/202, 190-203, and the MAA, a stability in scores was observed across the evaluation periods, and all results indicated no decreases in patient age-appropriate development or detriments to QoL associated with cerliponase alfa treatment. This is reflective of the personal experiences shared by patient advocates during the July 2023 advisory board (13). Advocates noted that since beginning treatment with cerliponase alfa, some patients have learned new words and gained confidence. Advocates also agreed that although patients may slowly decline, their mental health is very good, and one patient was noted to have become less distressed following starting cerliponase alfa treatment. There


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was a consensus that patient, parent, and sibling QoL was significantly improved as a direct result of cerliponase alfa treatment.

### B.2.12.5. Cerliponase alfa safety summary

Since HST12, the addition of safety data from the completion of 190-201/202, 190-203, and the long-term safety data from studies 190-501, 190-502, and 190-504 have all validated that the administration of cerliponase alfa is generally safe and well tolerated. An acceptable safety profile for long-term administration of cerliponase alfa in patients with CLN2 disease was confirmed across all three long-term studies.

### B.2.12.6. Natural history comparator validation

The open-label design and the lack of a comparator arm throughout the clinical evidence base was a result of ethical and practical considerations of ICV insertion in patients receiving placebo. Nevertheless, as shown in HST12, the matched analyses with NH controls was a robust technique used to mitigate the lack of a comparator arm, with matched results confirmed to be robust via multiple sensitivity analyses; which varied the populations being examined, the methods of analysis and the criteria used to match NH and treated patients. Baseline characteristics were well matched across all studies, except for sex, however as gender is not associated with CLN2 progression this was not considered problematic. Results based on matching were similar to unmatched analyses (Appendix O) and each analysis supported the underlying primary analysis. The treatment effect of cerliponase alfa was shown to be durable, with reduced disease progression, stable, or even improved outcomes in the participants treated with 300 mg every other week for over six years vs steady and almost uniformly progressive clinical decline in the NH population. As previously described, the external DEM-CHILD-RX study further validated the NH matched outcomes across the other effectiveness studies (Section B.2.6.6; Appendix P).

### B.2.12.7. Conclusions

The clinical development programme for cerliponase alfa provides evidence of clinical benefit with potential to stabilise CLN2 disease in patients diagnosed at earliest symptoms, and delay CLN2 disease progression in patients irrespective of starting ML score. This benefit therefore impacts HRQoL for patients with CLN2 of all ages and across all stages of disease, irrespective of baseline CLN2 Clinical Rating Scale ML score, and participant genotype. Cerliponase alfa is a highly innovative, breakthrough technology which, since becoming routinely available in 2019, has represented a step-change in the management of CLN2 disease.


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Since HST12, meaningful data has become available to support cerliponase alfa in the treatment of CLN2. Although the supportive clinical trials all comprise small patient numbers, patients have largely been recruited from the US and European sites, including the UK, and are representative of patients with CLN2 seen in UK clinical practice. For comparative analyses, study participants were matched to NH patients on criteria deemed likely to influence further disease course. Note that the baseline characteristics of study participants across trials are also very similar to those seen in the NH population.

The open-label design and the lack of a comparator arm are major limitations of the clinical evidence supporting this reappraisal. However, CLN2 is an extremely rare, life-limiting condition, and there was no pharmacological treatment approved for use that targets the underlying cause of CLN2 disease prior to cerliponase alfa. Consequently, the limitations of study design and methodology, coupled with the small sample size across all studies, are inevitable features of undertaking a clinical study for an active treatment for patients with a rare life-threatening disease, in an area of high unmet need.


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## B.3. Cost effectiveness

- A cost-effectiveness model was developed for the original NICE submission in 2019, comparing cerliponase alfa with standard of care (SoC) for the treatment of patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease.
- The following elements of the original cost-effectiveness model have been updated for the 2024 resubmission:
  - Baseline age and health state distribution
  - Transition probabilities and stabilisation assumptions
  - Progressive symptom rates
  - Adverse event rates
  - Infection rates
  - Mortality assumptions
  - Vision loss assumptions
  - Caregiver and sibling disutility
  - Scenario analyses for utility values
  - Adherence rate
  - Health state resource use
  - Residential care use
  - Requirements for behavioural/psychiatric support
  - Mapping algorithm between EQ-5D-5L and EQ-5D-3L
  - General population utility values
  - Life tables
  - Unit costs
  - Corrections for minor errors.
- The analysis is structured as a Markov model, with ten health states defined based on ML score and other key clinical characteristics
- Within each health state, the cost and quality of life (QoL) impact of progressive symptoms and adverse events (AEs), and the QoL impact on caregivers and siblings is considered
  - Transition probabilities for cerliponase alfa were derived from Study 190-203 and expert clinical opinion; transitions for the SoC arm are based on Study 190-901 (natural history study) and expert clinical opinion; scenario analyses consider transition probabilities based on pooled data from the clinical trial programme
  - Health state utility values were derived from a bespoke utility study in which vignettes describing the modelled health states were developed, validated by a clinical expert, and sent to eight clinical experts who completed the EQ-5D-5L questionnaire as a proxy for patients experiencing the health states; a scenario analysis considers EQ-5D-5L data from the managed access agreement (MAA)
  - Costs and resource use data were identified through a systematic literature review (SLR) and were implemented from a National Health Service (NHS) and personal social services (PSS) perspective. Where cost data were not available, expert clinical opinion informed the assumptions used for these inputs
  - In the base-case analysis, cerliponase alfa is associated with discounted incremental costs and quality-adjusted life years (QALYs) of [redacted] and 17.35, respectively, compared with SoC, resulting in an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY.


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- Cerliponase alfa is associated with 36.25 additional undiscounted QALYs compared with SoC; a QALY weighting of £300,000 therefore applies
- Probabilistic sensitivity analysis was performed and associated with incremental QALYs of 17.78 and incremental costs of [redacted], resulting in a probabilistic ICER of [redacted] per QALY
- Deterministic sensitivity analysis identified parameters associated with transitions in the cerliponase alfa arm to be the key drivers of cost-effectiveness
- Scenario analyses explored a range of assumptions, including age and health state distribution at model entry, source of transition probabilities, and the duration of stabilisation. Scenario analysis resulted in an ICER range of [redacted] to [redacted] per QALY vs SoC.

### B.3.1. Published cost-effectiveness studies

An SLR was conducted to identify cost-effectiveness studies from the published literature. A summary of the included cost-effectiveness studies and HTA submissions relevant to the decision problem is provided in Table 36. A complete description of the SLR methods and results is presented in Appendix G.


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**Table 36: Summary of included cost-effectiveness studies**

| Study, Year | Intervention/ comparator | Summary of model | Patient population | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| Gutić 2023 (85) | Cerliponase alfa vs BSC | This study was a cost-utility discrete event simulation model comparing cerliponase alfa and BSC (defined as symptomatic therapy of disease complications) from a payer perspective, with a 40-year time horizon and a one-month cycle length.<br><br>A 3.5% discount rate was applied to costs and benefits from the second year onwards.<br><br>Nine health states were included:<br>• Diagnosis of CLN2 established<br>• Epilepsy<br>• Abnormal behaviour<br>• Fall<br>• Dementia<br>• Adverse effect of treatment<br>• Inability to communicate<br>• Vision loss<br>• Death | Patients with CLN2 of both sexes, of any age, and with progressive disease | • Cerliponase alfa: 7.28 (99% CI: ±0.05)<br>• BSC: 5.67 (99% CI: ±0.05) | Total costs (RSD)<br>• Cerliponase alfa: 512,815,491 RSD (99% CI: ±12,231,522)<br>• BSC: 6,294,828 RSD (99% CI: ±329,444) | Cerliponase alfa vs BSC: 329,685,221 (99% CI: ±151,464,334) |
| SMC2286 2020 (55) | Cerliponase alfa vs SoC | This HTA submission presented a cost-utility Markov model comparing cerliponase alfa with SoC (defined as symptomatic and palliative management of generalised tonic-clonic seizures and loss of motor control and feeding) from a health and social care perspective for costs and a patient, sibling, and carer perspective for benefits, with a 95-year time horizon and a two week cycle length.<br><br>The discount rate was not reported.<br><br>Ten health states were included: | Patients with CLN2 | Redacted | Redacted | Redacted |


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| Study, Year | Intervention/ comparator | Summary of model | Patient population | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| | | • HS 1–7: based on CLN2 Clinical Rating scores<br>• HS 8: Complete vision loss<br>• HS 9: Palliative care<br>• HS 10: Death | | | | |
| CADTH 2019 (86) | Cerliponase alfa vs BSC | This HTA submission presented a cost-utility Markov model comparing cerliponase alfa and BSC from a payer perspective, with a 95-year (lifetime) time horizon and a two-week cycle length.<br><br>A 1.5% discount rate was applied to costs and benefits.<br><br>Ten health states were included:<br>• HS 1–7: based on combined scores from the motor and language domains of the CLN2 Clinical Rating Scale<br>• HS 8: Score of 0 on the CLN2 Clinical Rating Scale + complete vision loss<br>• HS 9: Score of 0 on the CLN2 Clinical Rating Scale + complete vision loss + requiring palliative care<br>• HS 10: Death | Patients of any age with a confirmed diagnosis of CLN2 disease | Incremental QALYs, cerliponase alfa vs BSC : 10.19 | Incremental costs (CAD), cerliponase alfa vs BSC: $18,446,778 | $1,811,059 |

Abbreviations: BSC, best supportive care; CAD, Canadian dollar; CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; HS, health state; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RSD, Dinars of the Republic of Serbia; SMC, Scottish Medicines Consortium; SoC, standard of care


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## B.3.2. Economic analysis

A cost-effectiveness model (CEM) was developed to support the original company submission to NICE (HST12) for cerliponase alfa in CLN2 disease. For this reappraisal, following the availability of new data and additional insight from CLN2 clinical experts, the following elements of the CEM have been updated:

- Baseline age and health state distribution
- Transition probabilities and stabilisation assumptions
- Progressive symptom rates
- Adverse event rates
- Infection rates
- Mortality  assumptions
- Vision loss assumptions
- Caregiver and sibling disutility
- Scenario analyses for utility values
- Adherence rate
- Health state resource use
- Residential care use
- Requirements for behavioural/psychiatric support
- Mapping algorithm between EQ-5D-5L and EQ-5D-3L
- General population utility values
- Life tables
- Unit costs
- Corrections for minor errors.


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### B.3.2.1. Patient population

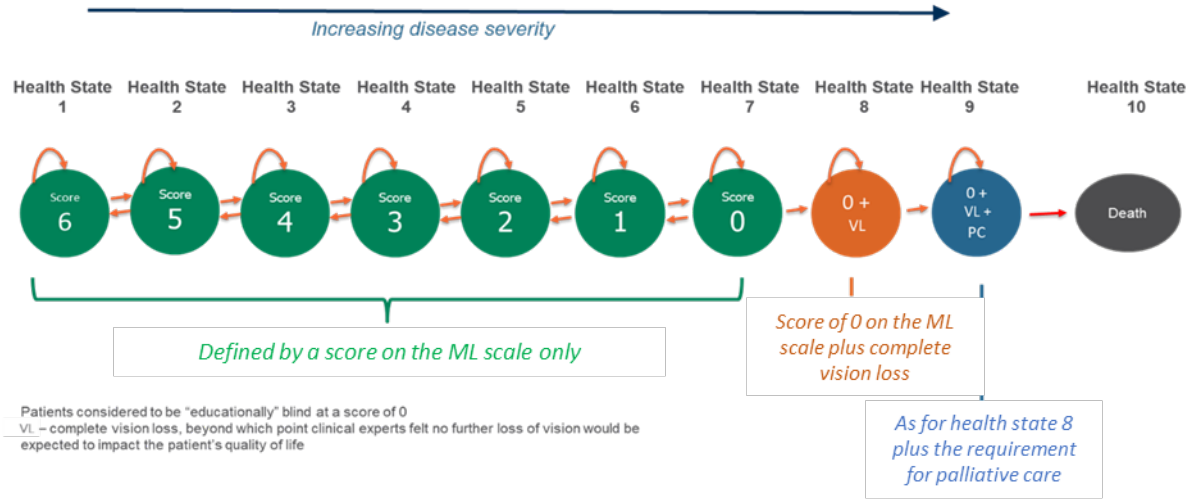
In line with the licensed indication for cerliponase alfa and the scope defined by NICE, the cost-effectiveness analysis considers patients with a confirmed diagnosis of CLN2 disease (24).

### B.3.2.2. Model structure

For this reappraisal, the economic model structure was validated by CLN2 clinical experts in a July 2023 advisory board and remains unchanged from HST12 (39). The economic analysis is structured as a Markov model comprised of ten mutually exclusive health states defined by ML score, vision loss, and the requirement for palliative care. A Markov structure was selected to capture the chronic and progressive nature of CLN2 disease. A model schematic is presented in Figure 18.

A cycle length of 2 weeks was assumed with half-cycle correction applied using the life table method; a cycle length of 2 weeks was considered sufficiently short to capture progression in ML score and reflects the administration frequency of cerliponase alfa.

**Figure 18: Model schematic**




Abbreviations: ML, motor and language; PC, palliative care; VL, vision loss.

A description of the modelled health states is presented in Table 37; further detail on ML score is provided in Section B.1. The use of these health states and their definitions, was validated by clinical experts with experience of CLN2 disease and cerliponase alfa.


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In each cycle, patients may remain in the same state, progress to a more severe state, or improve and move to a less severe state[a], with the exception that once patients reach health state 8, they can no longer return to a previous health state (39).

Within each health state, the following were considered:

- The cost and QoL impact of progressive symptoms[b]
- The cost and QoL impact of AEs
- The QoL impact on caregivers
- The QoL impact on siblings.

**Table 37: Health states**

| Health state | ML score | Additional characteristics |
|---|---|---|
| 1 | 6 | – |
| 2 | 5 | – |
| 3 | 4 | – |
| 4 | 3 | – |
| 5 | 2 | – |
| 6 | 1 | – |
| 7 | 0 | – |
| 8 | 0 | Complete vision loss (VL)† |
| 9 | 0 | Complete vision loss and requirement for palliative care (VL/PC) |
| 10 | NA | Death |

†Note that although complete vision loss is not modelled to occur until health state 8, the utility analysis (Section B.3.4) incorporates problems recognising objects at distance in health state 5, the inability to recognise objects other than those immediately ahead in health state 6, and functional blindness in health state 7.
Abbreviations: ML, motor language; NA, not applicable; PC, palliative care; VL, vision loss.

### B.3.2.3. Features of the economic analysis

An overview of the features of the economic analysis is presented in Table 38.

[a] In the SoC arm, there were insufficient transitions to less severe states to reliably inform these transitions; these transition probabilities are therefore assumed to be zero (Section B.3.3.2).

[b] Modelled progressive symptoms include seizures/epilepsy, reported distress, dystonia, myoclonus, musculoskeletal pain, and the requirement for a feeding tube.


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**Table 38: Features of the economic analysis**

| Factor | Original appraisal | Current evaluation | |
|---|---|---|---|
| | HST12 (cerliponase alfa original appraisal)† | Chosen values | Justification |
| Time horizon | Lifetime assuming a maximum age of 100 years | Lifetime assuming a maximum age of 100 years | A lifetime time horizon was selected as cerliponase alfa is expected to be associated with differential costs and outcomes over the lifetime of the individual, and NICE guidance states that the time horizon should be long enough to reflect all important difference in costs and outcomes between the technologies being compared (87) |
| Model cycle length | 2 weeks | 2 weeks | A 2-week cycle length was considered sufficiently short to capture progression in ML score and reflects the administration frequency of cerliponase alfa |
| Half cycle correction | Applied | Applied | To account for events and transitions that occur at any point in the 2-weekly modelled cycle |
| Discounting | 3.5% for costs and benefits | 3.5% for costs and benefits | In line with the NICE reference case (87) |
| Source of utilities | Derived from a bespoke utility study using vignettes, validated by a clinical expert, and completed via proxy using the EQ-5D-5L (37) and mapped to the EQ-5D-3L using the mapping function published by Van Hout (88) | Derived from a bespoke utility study using vignettes, validated by a clinical expert, and completed via proxy using the EQ-5D-5L (37) and mapped to the EQ-5D-3L using the mapping function based on the EEPRU dataset and published by Hernández-Alava (89) | Utility data collected in the clinical trial programme and the MAA were informed by small sample sizes and did not include data for the most severe health states or for the SoC arm. Therefore, data based on questionnaires completed by a proxy (CLN2 clinical experts) were utilised in the base case. A scenario analysis considers utility values from the MAA, with assumptions made for the SoC arm and for the most severe health states.<br><br>The mapping algorithm to derive EQ-5D-3L values was updated from the algorithm published by Van Hout to the mapping function based on the EEPRU dataset and published by Hernández Alava in line with NICE guidance (87, 88, 90) |
| Source of resource use | Derived from clinical expert opinion in the 2016 Delphi panel (91) and published literature | Derived from:<br>• Clinical expert opinion in the 2016 Delphi panel (91) and 2023 July and November clinical advisory boards (39, 42)<br>• Published literature. | Per original company submission and updated clinical expert opinion in 2023 |


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| Factor | Original appraisal | Current evaluation | |
|---|---|---|---|
| | HST12 (cerliponase alfa original appraisal)† | Chosen values | Justification |
| Source of costs | NHS reference costs 2015/16, BNF (accessed in 2017), eMIT (accessed in 2017), PSSRU 2016, published literature. | NHS reference costs 2021/22, BNF (accessed in 2023), eMIT (accessed in 2023), PSSRU 2022 (92), literature and inflated to 2021/22 prices using the PSSRU 2022 (93) | Per NICE reference case and original company submission |

†Note that 'Original appraisal' refers to the final decision-making model.
Abbreviations: BNF, British National Formulary; CLN2, neuronal ceroid lipofuscinosis type; DSU, Decision Support Unit; EEPRU, Policy Research Unit in Economic Evaluation of Health and Care Interventions; eMIT, drugs and pharmaceutical electronic market information tool; MAA, managed access agreement; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit.


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### B.3.2.4. Intervention technology and comparators

#### B.3.2.4.1. Intervention

The intervention considered is cerliponase alfa administered by ICV infusion once in every 14-day cycle, in line with the SmPC (24). The dose required for each age group is presented in Table 39.

In the CEM, in the absence of discontinuation data for cerliponase alfa, patients receiving cerliponase alfa are assumed to discontinue treatment when their ML score reaches 1; following discontinuation, transition probabilities and utility values for the SoC arm are assumed to apply. Discontinuation at an ML score of 1 was assumed as it is anticipated that patients have progressed such that continued treatment with cerliponase alfa is unlikely to improve motor and language capabilities.

**Table 39: Cerliponase alfa dosing by age group**

| Age group | Dose (mg) |
|---|---|
| Birth to <6 months | 100 |
| 6 months to <1 year | 150 |
| 1 year to <2 years | 200 (first four doses)<br>300 (subsequent doses) |
| 2 years and older | 300 |

#### B.3.2.4.2. Comparator

The comparator considered in the analysis is established clinical management without cerliponase alfa (SoC).

## B.3.3. Clinical parameters and variables

Clinical parameters and variables included in the CEM include:

- Baseline characteristics & health state distribution
- Transition probabilities
- Progressive symptoms
- AEs
- Mortality.


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### B.3.3.1. Baseline characteristics & health state distribution

Study 190-201 was comprised of 15 (62.5%) and nine (37.5%) female and male participants, respectively; due to the small study size (N=24), clinical expert opinion was sought in advance of the original submission, and it was concluded there is no difference in CLN2 prevalence by sex (39). The proportion of CLN2 patients who are male was therefore assumed to be 50%, and this assumption has been maintained for this resubmission.

Following the original submission to NICE (HST12), new data on the age and distribution of patients across health states at initiation of cerliponase alfa treatment is available from the following sources:

- Study 190-203
- New patents in the MAA (i.e. MAA patients who did not transition from the clinical trial programme).

However, it is anticipated that age and ML score at initiation of cerliponase alfa will decrease and improve, respectively, over time due to:

- Earlier diagnosis of CLN2 disease:
    - Awareness of CLN2 disease amongst clinicians is expected to increase following availability of cerliponase alfa, resulting in earlier diagnosis. In addition, there is an ongoing pilot project for newborn screening in the UK (43), and clinical experts at a UK advisory board confirmed that national newborn screening for CLN2 is possible within the next 5 years (39).
- Initiation of treatment more quickly following diagnosis:
    - Patients in Study 190-203 initiated treatment an average of 26.17 (n=7[c]) months following diagnosis
    - For some patients in the studies and including the MAA, it is expected that cerliponase alfa was not a treatment option at the time of diagnosis

[c] Age at diagnosis was reported for 7 out of the total 14 patients in the ITT population of Study 190-203.


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- Following the availability and an increasing awareness of cerliponase alfa, it is anticipated that clinicians would initiate treatment as soon as possible following diagnosis.

In addition, the COVID-19 pandemic is expected to have delayed both diagnosis and initiation of treatment in some patients. The base-case analysis therefore uses the baseline age and health state distribution of patients in Study 190-203 who initiated treatment at age less than 3 years; this population is expected to best reflect the population of patients who will receive cerliponase alfa in the near future.

For completeness, scenario analyses consider baseline age and health state distributions based on the full population of Study 190-203, and new patients from the MAA. However, analyses using these sources are considered conservative, given that time to both diagnosis and initiation of treatment are expected to decrease, and given the impact of the COVID-19 pandemic.

The baseline age and health state distributions used in the model base case and scenario analyses are presented in Table 40 and Table 41.

**Table 40: Age at model entry**

| | Starting distribution (%) | | |
|---|---|---|---|
| | Base case – Study 190-203 (<3 years) | Scenario – Study 190-203 | Scenario – MAA new patients |
| Age | 2.00 | 3.07 | 4.76 |

Abbreviations: MAA, managed access agreement.

**Table 41: Health state distribution at model entry**

| Health state | Starting distribution (%) | | |
|---|---|---|---|
| | Base case – Study 190-203 (<3 years) | Scenario – Study 190-203 | Scenario – MAA new patients |
| 1 | 87.5% | 50.0% | 18.2% |
| 2 | 12.5% | 7.1% | 13.6% |
| 3 | 0.0% | 21.4% | 45.5% |
| 4 | 0.0% | 7.1% | 13.6% |
| 5 | 0.0% | 7.1% | 9.1% |
| 6 | 0.0% | 7.1% | 0.0% |
| 7 | 0.0% | 0.0% | 0.0% |
| 8 | 0.0% | 0.0% | 0.0% |
| 9 | 0.0% | 0.0% | 0.0% |

Abbreviations: MAA, managed access agreement.


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### B.3.3.2. Transition probabilities

#### B.3.3.2.1. Health state 1-7 transition probabilities

In the population of patients who entered Study 190-203 at less than 3 years of age, seven patients initiated treatment at an ML score of 6 (health state 1), and one patient initiated treatment at an ML score of 5 (health state 2). Of the 8 patients less than 3 years of age, five patients had follow-up in Study 190-504, with the remaining patients lost to follow-up. For the patients who initiated treatment in ML 6, no changes were observed in ML score over a maximum of 6 years of study follow-up. No data are therefore available from Study 190-203 on how these patients transition between health states[d].

Patients who initiate treatment at ML 6 are therefore modelled to stay at ML 6 for the first 6 years of cerliponase alfa treatment, after which they are assumed to transition between health states at half the rate observed for patients initiating treatment in other ML scores (i.e. a 50% reduction). A clinical expert advised that a 50% reduction may be conservative, given that no change was observed in the first 6 years; scenario analyses are therefore considered in which reductions of 75% and 100% are applied.

In order to inform transition probabilities for cerliponase alfa patients who initiate treatment at an ML score of 5 or lower, data from Study 190-203, Study 190-201/202, and the MAA were pooled. To derive transition probabilities for SoC patients, a one-to-one matching was applied vs Study 190-901. In the base case, only transitions from Study 190-203 (and the matched patients from Study 190-901) were used, to align with the starting population; scenario analyses considered:

- All patients from the pooled studies for cerliponase alfa and Study 190-901 one-to-one matched patients for SoC
- 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

The analysis in which transition probabilities are estimated separately for <6 months from baseline and ≥6 months from baseline was performed to determine the impact of any delay in the full treatment effect of cerliponase alfa being realised.

[d] Any observations of transitions from ML 6 in Study 190-203 reflect data for patients who started with ML 5 and experienced fluctuations between ML 6 and ML 5.


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The MSM package in R (using a multistate modelling framework) was used to generate transition intensities for each of the cerliponase alfa and SoC arms based on the matched data; this approach was preferred to standard methods of calculation as it can account for differing follow-up and observation periods between patients and between studies. Transition intensities were converted to transition probabilities using the standard formula: $p = 1 - \exp(-rt)$.

For simplicity, it was assumed that patients can only move one health state in a model cycle; where movements of two or more states were observed in the data, the MSM package includes additional one-state transitions at interim time points.

Transition probabilities for the model base case and scenario analyses are presented in Table 42 and Table 43 for cerliponase alfa and SoC, respectively; transitions from health state 6 and health state 7 were taken from the pooled analysis in all scenarios, as very few transitions into/from these health states were observed in the clinical data.

**Table 42: Transition probabilities in states 1–7, cerliponase alfa**

| Transition | Transition probabilities | | | |
|---|---|---|---|---|
| | Base case – Study 190-203 | Scenario – All patients | Scenario – All patients (piecewise at 6 months) | |
| | | | <6 months | ≥6 months |
| HS7 to HS6 | 6.1%† | 6.1% | 6.1%† | 6.1%† |
| HS6 to HS7 | 1.5%† | 1.5% | 1.5%† | 1.5%† |
| HS6 to HS5 | 2.7%† | 2.7% | 2.7%† | 2.7%† |
| HS5 to HS6 | 2.1% | 2.1% | 2.3% | 0.1% |
| HS5 to HS4 | 1.1% | 1.3% | 1.1% | 0.0% |
| HS4 to HS5 | 6.4% | 3.7% | 3.7% | 0.1% |
| HS4 to HS3 | 7.2% | 2.5% | 2.2% | 0.1% |
| HS3 to HS4 | 6.6% | 5.8% | 5.2% | 0.3% |
| HS3 to HS2 | 0.9% | 0.6% | 0.6% | 0.0% |
| HS2 to HS3 | 5.4% | 6.7% | 6.2% | 0.4% |
| HS2 to HS1 | 5.8% | 2.6% | 2.7% | 0.1% |
| HS1 to HS2 | 0.5% | 0.7% | 0.7% | 0.0% |

†Assumed equivalent to transition probabilities for the pooled analysis.
Abbreviations: HS, health state.

**Table 43: Transition probabilities in states 1–7, SoC**

| Transition | Transition probabilities | | | |
|---|---|---|---|---|
| | Base case – Study 190-203 | Scenario – All patients | Scenario – All patients (piecewise at 6 months)† | |
| | | | <6 months | ≥6 months |
| HS6 to HS7 | 7.1% | 7.6% | 7.6% | 7.6% |
| HS5 to HS6 | 10.1% | 9.2% | 9.2% | 9.2% |


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| Transition | Transition probabilities | | | |
|---|---|---|---|---|
| | Base case – Study 190-203 | Scenario – All patients | Scenario – All patients (piecewise at 6 months)† | |
| | | | <6 months | ≥6 months |
| HS4 to HS5 | 11.6% | 11.1% | 11.1% | 11.1% |
| HS3 to HS4 | 12.1% | 7.6% | 7.6% | 7.6% |
| HS2 to HS3 | 5.6% | 7.3% | 7.3% | 7.3% |
| HS1 to HS2 | 4.6% | 6.3% | 6.3% | 6.3% |

†Note that SoC transition probabilities are not assumed to differ based on time since baseline; the transition probabilities for this scenario are therefore equivalent to the 'All patients' scenario.
Abbreviations: HS, health state.

#### B.3.3.2.2. Health state 7–9 transition probabilities

Progressive transitions in health states 7–9 were derived from a 2016 Delphi panel in which experts provided estimates for SoC (91). In the absence of equivalent information for cerliponase alfa, a conservative assumption was made to assume equal transition probabilities for cerliponase alfa and SoC. The mean time to vision loss, mean time from loss of vision to requiring palliative care, and time receiving palliative care before disease-related mortality were estimated in order to derive 2-week transition probabilities (Table 44)

**Table 44: Transition probabilities in states 7–9, cerliponase alfa and SoC**

| | From state – to state | Time to event (weeks) | 2-week transition probability | Reference |
|---|---|---|---|---|
| Time to loss of vision | 7–8 | 52 | 0.038 | Delphi panel (91) |
| Time from loss of vision to requiring palliative care | 8–9 | 52 | 0.038 | |
| Time receiving palliative care before disease-related mortality | 9-10 | 52 | 0.038 | |

Abbreviations: SoC, standard of care.

### B.3.3.3. Progressive symptoms

Progressive symptoms not captured by ML score, and their associated costs and disutilities, were modelled within the model health states. Progressive symptoms considered in the analysis were selected based on the publication by Williams 2017[e] (15), and validated in the Delphi panel (91) and a clinical advisory board in 2023 (39) and include:

- Distress
- Dystonia

[e] Musculoskeletal pain was included as an additional symptom following the July 2023 advisory board.


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- Myoclonus
- Requirement of a feeding tube
- Seizures/epilepsy
- Musculoskeletal pain.

For all progressive symptoms, the relevant proportions informed by the Delphi panel in 2016 were validated and updated as required in a series of advisory boards with clinical experts held in 2023 (39, 42, 91). The proportions of patients experiencing each progressive symptom were derived for each treatment arm by health state.

Generally, clinicians reported the proportion with progressive symptoms to be lower in patients treated with cerliponase alfa vs SoC for milder health states, with estimates converging between arms as the disease progresses.

The proportion with the progressive symptoms distress, seizures, dystonia, myoclonus, musculoskeletal pain, and requirement of a feeding tube are presented in Table 45 to Table 50.

**Table 45: Proportion of patients experiencing distress[f]**

| Health state | % experiencing distress | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | 2% | 5% |
| 2 | 5% | 19% |
| 3 | 10% | 20% |
| 4 | 20% | 30% |
| 5 | 30% | 40% |
| 6 | 40% | 50% |
| 7 | 50% | 60% |
| 8 | 70% | 70% |
| 9 | 70% | 70% |

Abbreviations: SoC, standard of care.

**Table 46: Number of seizures and requirement of rescue medication**

| Health state | Overall number of seizures | | Number of seizures that require rescue medication | |
|---|---|---|---|---|
| | Cerliponase alfa | SoC | Cerliponase alfa | SoC |
| 1 | 1 to 5 | 5 to 10 | 1 to 5 | 1 to 5 |

[f] Proportion of patients with distress was defined as the presence of distress cause by CLN2 excluding distress associated with cerliponase alfa infusions. Distress associated with cerliponase alfa infusion is assumed to be managed as part of the hospital infusion.


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| Health state | Overall number of seizures | | Number of seizures that require rescue medication | |
|---|---|---|---|---|
| | Cerliponase alfa | SoC | Cerliponase alfa | SoC |
| 2 | 1 to 5 | >10 | 1 to 5 | 1 to 5 |
| 3 | 5 to 10 | >20 | 1 to 5 | 5 to 10 |
| 4 | 5 to 10 | >50 | 1 to 5 | 5 to 10 |
| 5 | 10 to 20 | >50 | 1 to 5 | 5 to 10 |
| 6 | >20 | >100 | 1 to 5 | 5 to 10 |
| 7 | >20 | >100 | 5 to 10 | >10 |
| 8 | >20 | >100 | 5 to 10 | >10 |
| 9 | >20 | >100 | >10 | >10 |

Abbreviations: SoC, standard of care.

**Table 47: Proportion of patients experiencing dystonia[g]**

| Health state | % experiencing dystonia | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | 0% | 0% |
| 2 | 0% | 10% |
| 3 | 20% | 40% |
| 4 | 40% | 80% |
| 5 | 50% | 100% |
| 6 | 100% | 100% |
| 7 | 100% | 100% |
| 8 | 100% | 100% |
| 9 | 100% | 100% |

Abbreviations: SoC, standard of care.

**Table 48: Proportion of patients experiencing myoclonus[h]**

| Health state | % experiencing myoclonus | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | 0% | 20% |
| 2 | 10% | 40% |
| 3 | 50% | 70% |
| 4 | 80% | 90% |
| 5 | 100% | 100% |
| 6 | 100% | 100% |
| 7 | 100% | 100% |
| 8 | 100% | 100% |
| 9 | 100% | 100% |

Abbreviations: SoC, standard of care.

[g] Proportion of patients with dystonia was specified as the proportion of patients with dystonia such that medication is required.

[h] Proportion of patients with myoclonus was defined as the proportion of patients experiencing non-epileptical myoclonus such that medication is required.


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**Table 49: Proportion of patients experiencing musculoskeletal pain[i]**

| Health state | % experiencing musculoskeletal pain | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | 5% | 5% |
| 2 | 10% | 20% |
| 3 | 15% | 30% |
| 4 | 30% | 50% |
| 5 | 40% | 60% |
| 6 | 60% | 80% |
| 7 | 80% | 90% |
| 8 | 80% | 90% |
| 9 | 80% | 90% |

Abbreviations: SoC, standard of care.

**Table 50: Proportion of patients requiring a feeding tube[j]**

| Health state | % requiring a feeding tube | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | 0% | 0% |
| 2 | 0% | 10% |
| 3 | 0% | 50% |
| 4 | 0% | 70% |
| 5 | 20% | 100% |
| 6 | 80% | 100% |
| 7 | 100% | 100% |
| 8 | 100% | 100% |
| 9 | 100% | 100% |

Abbreviations: SoC, standard of care.

### B.3.3.4. Vision loss

Administration of cerliponase alfa using an ICV device is not expected to have an effect on the retina therefore, progressive vision loss is anticipated in all modelled patients. In order to capture the cost impact of vision loss with CLN2, it was assumed that all patients in health states 7–9 experienced vision loss. This is to align with the health state utility vignettes, which describe patients in health state 7 as functionally blind. In health states 1–6, it was assumed that the proportion of patients with vision loss increases linearly from 0% at age 6 to 100% at age 20; this is aligned with the approach to modelling the disutility of vision loss

[i] Musculoskeletal pain was defined as the presence of musculoskeletal pain, related to bed-ridden status, spasticity, scoliosis, or abnormal movements/postures.

[j] Proportion of patients requiring a feeding tube was defined as the proportion of patients expected to require a feeding tube including all patients who have had a feeding tube inserted, irrespective of whether the feeding tube is yet in use.


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from the original appraisal, the assumptions of which were re-validated in a July 2023 clinical advisory board (Section B.3.4.5.1) (39).

### B.3.3.5. AEs

The cost and utility impact of the most common study drug-related AEs in Study 190-202 were modelled in the cerliponase alfa arm of the model.

The proportion of patients experiencing each event is presented in Table 51 and derived from the Study 190-202 final Clinical Study Report (CSR) (44). As SoC was defined as established clinical management without cerliponase alfa, the SoC arm is not associated with AEs.

**Table 51: Proportion experiencing AEs**

| AE | % experiencing event | |
|---|---|---|
| | Cerliponase alfa | SoC |
| Pyrexia | 45.8% | 0.0% |
| Hypersensitivity | 41.7% | 0.0% |
| Headache | 12.5% | 0.0% |
| Vomiting | 25.0% | 0.0% |

Abbreviations: AE, adverse event; SoC, standard of care.

### B.3.3.6. Mortality

In line with the model structure (Section B.3.2.2), patients in health state 9 transition into the death state based on transition probabilities estimated by clinical experts in the Delphi panel (Section B.3.3.2). It was assumed that the probability of transitioning to death from health state 9 would be constant, and an exponential function with a mean of 52 weeks was fitted and used to derive this transition probability (Section B.3.2.3). No additional mortality due to neurodisability was modelled (19, 94), given that no deaths have been observed in the cerliponase alfa trial programme in which neurodisability was the cause.

In all health states, age-related background mortality is applied based on life tables for England and Wales for 2018-2020 (95).

## B.3.4. Measurement and valuation of health effects

### B.3.4.1. Health-related quality of life data from clinical trials

HRQoL was assessed in studies 190-201/202, 190-203, and in data collected during the MAA. The following HRQoL instruments were completed by a patient proxy (parent/guardian):

- PedsQL – Parent Reports (various ages) and Family Impact Module


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- CLN2-QL – a CLN2 disease-specific QoL instrument
- EQ-5D-5L.

### B.3.4.2. Mapping

Mapping of HRQoL outcomes was not required.

#### B.3.4.2.1. Health state utility values

Utility values from the data collected in Study 190-201/202 (limited amounts of EQ-5D-5L and PedsQL data) were not used in the model, due to the small number of observations and the inability to obtain utility values for all health states in the model. In addition, no data were available for SoC patients.

Base-case health state utility values were derived from Gissen et al, 2021, a bespoke utility study in CLN2 disease (37) in which descriptions of the health states (vignettes) were generated based on:

- The most prevalent combinations of the motor and language domain scores defining ML scores
- Details of the other progressive symptoms experienced in each health state.

Eighteen vignettes were produced, representing each health state for both cerliponase alfa and SoC treatment arms. To ensure the vignettes accurately represent CLN2 disease progression, the vignettes were validated by a clinical expert with experience of CLN2 disease and cerliponase alfa treatment in a Delphi panel conducted in 2016 (91). Vignettes are presented in Appendix S.

In the study, the vignettes were sent to eight clinical experts, who were asked to complete the EQ-5D-5L questionnaire as a proxy for patients with CLN2 disease. The study reported ‘excellent’ inter-reader agreement between vignettes using intraclass correlation values. The EQ-5D-5L values were mapped to EQ-5D-3L values using the Hernández Alava mapping algorithm to obtain the utility values, in line with NICE guidance (90). Male and female utility values were subsequently used to derive a weighted average health state utility based on the modelled proportion of male and female patients (Section B.3.3.1). Utility values used in the CEM are presented in Table 52.


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**Table 52: Base-case health state utility values – utility study, Gissen et al, 2021 (37)**

| Health state | Cerliponase alfa | | | SoC | | |
|---|---|---|---|---|---|---|
| | Male | Female | Weighted average | Male | Female | Weighted average |
| 1 | 0.975 | 0.973 | 0.974 | 0.987 | 0.985 | 0.986 |
| 2 | 0.766 | 0.755 | 0.761 | 0.734 | 0.723 | 0.728 |
| 3 | 0.630 | 0.625 | 0.627 | 0.529 | 0.526 | 0.527 |
| 4 | 0.399 | 0.388 | 0.394 | 0.282 | 0.270 | 0.276 |
| 5 | 0.333 | 0.326 | 0.330 | 0.074 | 0.060 | 0.067 |
| 6 | 0.200 | 0.194 | 0.197 | 0.049 | 0.036 | 0.043 |
| 7 | -0.111 | -0.118 | -0.115 | -0.335 | -0.331 | -0.333 |
| 8 | -0.171 | -0.182 | -0.176 | -0.325 | -0.326 | -0.326 |
| 9 | -0.193 | -0.200 | -0.197 | -0.359 | -0.358 | -0.359 |

Abbreviations: SoC, standard of care.

A scenario analysis is presented in which health state utility values for cerliponase alfa were derived from the MAA database, in which EQ-5D-5L data were collected every 6 months. EQ-5D-5L values were cross-walked to EQ-5D-3L values using the mapping algorithm outlined by Hernández Alava (90). As the sex for new MAA patients was not reported, separate mapping analyses were conducted for the overall MAA cohort assuming a 100% male population and a 100% female population. As 18–24 years is the lowest age group reported in the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset, this was used as a proxy for the overall MAA cohort. In the absence of utility values for either health state 8 or 9, and for SoC patients, the utility decrements from the study by Gissen et al, were assumed to apply to the observed values from the MAA database. The utility values used in the scenario analysis are presented in Table 53.

**Table 53: Scenario health state utility values – MAA†**

| Health state | Cerliponase alfa | | | SoC | | |
|---|---|---|---|---|---|---|
| | Male | Female | Weighted average | Male | Female | Weighted average |
| 1 | 0.862 | 0.861 | 0.862 | 0.874 | 0.873 | 0.873 |
| 2 | 0.651 | 0.643 | 0.647 | 0.621 | 0.611 | 0.616 |
| 3 | 0.667 | 0.661 | 0.664 | 0.416 | 0.414 | 0.415 |
| 4 | 0.542 | 0.528 | 0.535 | 0.169 | 0.158 | 0.164 |
| 5 | 0.417 | 0.405 | 0.411 | -0.039 | -0.052 | -0.045 |
| 6 | 0.288 | 0.263 | 0.276 | -0.064 | -0.075 | -0.070 |
| 7 | 0.073 | 0.027 | 0.050 | -0.448 | -0.443 | -0.445 |
| 8 | 0.013 | -0.037 | -0.012 | -0.438 | -0.438 | -0.438 |
| 9 | -0.010 | -0.055 | -0.032 | -0.472 | -0.470 | -0.471 |

†Note that one patient was excluded from the analysis as implausibly high utility values were recorded for a patient with ML score of 0.
Abbreviations: MAA, managed access agreement; SoC, standard of care.


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### B.3.4.3. Health-related quality of life studies

An SLR was conducted to identify HRQoL studies from the published literature. Three published studies and one SMC submission met the pre-defined inclusion criteria. A complete description of the SLR methods and identified studies is presented in Appendix H.

### B.3.4.4. Adverse reactions

For AEs occurring in the cerliponase alfa arm, disutilities were sourced from the literature. The annual QALY loss due to AEs was calculated, and, in the absence of AE rate change beyond the clinical trial, the rate of occurrence of AEs (Section B.3.3.5) was assumed to be constant throughout the model time horizon, in line with the dosing schedule of cerliponase alfa being unchanged throughout the model time horizon (Table 54).


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**Table 54: AE disutility**

| AE | Disutility | | AE duration (days) | | Annual occurrences of AE | | Total annual disutility |
|---|---|---|---|---|---|---|---|
| | Value | Reference | Value | Reference | Value | Reference | |
| Pyrexia | –0.11 | Beusterien 2010 (96) | 1.6 | Study 190-202 patient narratives (94) | 3.39 | Study 201/202, Patient Narratives (94) | –0.0016 |
| Hypersensitivity | –0.03 | Kauf 2010 (97) | 1 | Assumption | 0.72 | | –0.0001 |
| Headache | –0.12 | Maniadakis 2013 (98) | 1 | | 0.87 | | –0.0003 |
| Vomiting | –0.05 | Beusterien 2010 (96) | 1 | | 1.01 | | –0.0001 |

Abbreviation: AE, Adverse event.


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### B.3.4.5. Health-related quality of life data used in the cost-effectiveness model

#### B.3.4.5.1. Vision loss utility multiplier

Health states 8 and 9 are defined as having complete vision loss, and the vignettes for health state 7 assume functional blindness; however, progressive vision loss is expected in earlier states. Although this is captured in the vignettes supporting the utility study (Section B.3.4.2.1), clinical input in the original appraisal noted that vision loss is not expected to be ameliorated with cerliponase alfa. To account for the impact of progressive vision loss on HRQoL in health states 1–6, a utility multiplier was applied to all patients as follows:

- 1 for those aged <6 years
- 0.87 for those aged >20 years
- A linear decline between 1 and 0.87 for patients between 6 and 20 years.

The value of 0.87 reflects the QoL in patients with neovascular macular degeneration in the UK (99).

#### B.3.4.5.2. Caregiver and sibling disutility

**Caregiver disutility**

As a patient's CLN2 disease progresses, increasing levels of support are required from a combination of family and non-family caregivers. The number of caregivers per patient by health state, and the proportion of care that would be provided by family caregivers and non-family caregivers, was informed by the 2016 Delphi panel and presented in Table 55 (91).

**Table 55: Number of caregivers**

| Health state | Average number of caregivers required | Number of family caregivers | Number of non-family caregivers |
|---|---|---|---|
| 1 | 0.06 | 0.06 | 0 |
| 2 | 0.67 | 0.67 | 0 |
| 3 | 0.75 | 0.75 | 0 |
| 4 | 1 | 0.83 | 0.17 |
| 5 | 1 | 0.78 | 0.22 |
| 6 | 1 | 0.79 | 0.21 |
| 7 | 1.25 | 0.9375 | 0.3125 |
| 8 | 1.14 | 0.8322 | 0.3078 |
| 9 | 1.14 | 0.8322 | 0.3078 |


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In the original appraisal, caregiver disutility was derived from a report presenting the challenges of living with and caring for a child affected by CLN2 disease (12, 33). The UK EQ-5D-5L crosswalk score was compared with matched norms (age-group and gender) taken from Health Survey for England (2010), and it was found that UK caregivers had a significantly lower EQ-5D-5L score, with a difference of –0.108.

This disutility was not reported separately by patient ML score; the following assumptions were therefore made:

- The disutility for the first two health states was sourced from clinical expert opinion (91)
- For the remaining seven health states, disutility was assumed to increase linearly from 0, with –0.108 being applied to the midpoint of these remaining seven health states, to the proportion of caregivers that are family caregivers (Table 56).

**Table 56: Caregiver disutility, original company submission (2019, HST12)**

| Health state | Caregiver disutility | Source |
|---|---|---|
| 1 | –0.02 | Clinical expert opinion (91) |
| 2 | –0.025 | |
| 3 | –0.027 | Assumption of a linear progression in the health states after health states 1 and 2, with the value (–0.108) at the midpoint of those health states matching the value found in the study |
| 4 | –0.054 | |
| 5 | –0.081 | |
| 6 | –0.108 | 'Challenges of living with and caring for a child affected by CLN2 disease, a type of Batten disease' (p.132) (33) |
| 7 | –0.135 | Assumption of a linear progression in the health states after health states 1 and 2, with the value (–0.108) at the midpoint of those health states matching the value found in the study |
| 8 | –0.162 | |
| 9 | –0.189 | |

Abbreviations : CLN2, neuronal ceroid lipofuscinoses.

In an advisory board with clinical experts held in November 2023, caregiver disutility values were validated (42). Clinicians stated that patients treated with cerliponase alfa experience fewer progressive symptoms (even within the same health state) and may require less seizure rescue medication. Given this feedback, and that utility values differ between cerliponase alfa and SoC for patients, a 50% reduction in caregiver disutility was assumed for the cerliponase alfa arm. Modelled caregiver disutilities are presented in Table 57.


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**Table 57: Caregiver disutility, base case**

| Health state | Caregiver disutility | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | -0.01 | -0.02 |
| 2 | -0.01 | -0.03 |
| 3 | -0.01 | -0.03 |
| 4 | -0.03 | -0.05 |
| 5 | -0.04 | -0.08 |
| 6 | -0.05 | -0.11 |
| 7 | -0.07 | -0.14 |
| 8 | -0.08 | -0.16 |
| 9 | -0.09 | -0.19 |

Abbreviations: SoC, standard of care.

### Sibling disutility

In addition to caregiver disutility, sibling disutility was also modelled. Sibling disutility was applied across all but the first two health states, in line with guidance from clinical experts (91). The value for sibling disutility was obtained from a report on the challenges of living with and caring for a child affected by CLN2 disease (33). Child sibling utility values were found to be 0.91 on the Child Health Utility Instrument (CHU-9D); assuming children have a utility value of 1 under normal circumstances, a –0.09 decrement is applied.

In the absence of data on the patient's ML score when sibling utility values were measured, the following assumptions were made:

- No disutility applies in the first two health states
- In the remaining seven health states, disutility was assumed to increase linearly, with -0.09 applied to the midpoint of these remaining states (health state 6).

Modelled sibling disutility is presented in Table 58.


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**Table 58: Sibling disutility original company submission (2019, HST12)**

| Health state | Sibling disutility | Source |
|---|---|---|
| 1 | 0.000 | 'Challenges of living with and caring for a child affected by CLN2 disease, a type of Batten disease' (p.141) (33), with the assumption that no disutility is applied in the first two health states, with a linear progression in the following health states, with the value at the midpoint of the following health states being –0.090, the value in the study |
| 2 | 0.000 | |
| 3 | –0.023 | |
| 4 | –0.045 | |
| 5 | –0.068 | |
| 6 | –0.090 | |
| 7 | –0.113 | |
| 8 | –0.135 | |
| 9 | –0.158 | |

Abbreviations : CLN2, neuronal ceroid lipofuscinoses.

Similarly to caregiver disutility, sibling disutility values were validated with clinical experts in an advisory board held in November 2023 (42). As patients treated with cerliponase alfa are expected to experience fewer progressive symptoms than patients on SoC, the base-case assumes a 50% reduction in sibling disutility for the cerliponase alfa arm (Table 59).

**Table 59: Sibling disutility, base case**

| Health state | Caregiver disutility | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | 0.00 | 0.00 |
| 2 | 0.00 | 0.00 |
| 3 | -0.01 | -0.02 |
| 4 | -0.02 | -0.05 |
| 5 | -0.03 | -0.07 |
| 6 | -0.05 | -0.09 |
| 7 | -0.06 | -0.11 |
| 8 | -0.07 | -0.14 |
| 9 | -0.08 | -0.16 |

Abbreviations: SoC, standard of care.

The sibling disutility is applied to all siblings of patients with CLN2 disease. It is assumed a patient has 0.94 siblings, based on a BDFA survey showing there to be 32 siblings (without CLN2 disease) across an analysis of 34 CLN2 disease patients.

### B.3.4.6. Summary of utility values for cost-effectiveness analysis

A summary of utility values for cost-effectiveness analysis is presented in Table 60.


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**Table 60: Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (standard error) | 95% CI | Reference in submission (section and page number) | Justification |
|---|---|---|---|---|
| **Health state utility values** | | | | |
| Cerliponase alfa, health state 1 | 0.974 | 0.951, 0.997 | Section B.3.4.2.1, Page 143 | Utility values for cerliponase alfa and SoC were derived from a CLN2 utility study and mapped from EQ-5D-5L to EQ-5D-3L per the NICE reference case using the mapping function developed by the NICE DSU using the EEPRU dataset and published by Hernández-Alava et al. (90) |
| Cerliponase alfa, health state 2 | 0.761 | 0.741, 0.780 | | |
| Cerliponase alfa, health state 3 | 0.627 | 0.583, 0.672 | | |
| Cerliponase alfa, health state 4 | 0.394 | 0.299, 0.488 | | |
| Cerliponase alfa, health state 5 | 0.330 | 0.197, 0.462 | | |
| Cerliponase alfa, health state 6 | 0.197 | 0.063, 0.331 | | |
| Cerliponase alfa, health state 7 | –0.115 | -0.234, 0.005 | | |
| Cerliponase alfa, health state 8 | –0.176 | -0.301, -0.051 | | |
| Cerliponase alfa, health state 9 | –0.197 | -0.315, -0.078 | | |
| SoC, health state 1 | 0.986 | 0.986, 0.986 | | |
| SoC, health state 2 | 0.728 | 0.665, 0.792 | | |
| SoC, health state 3 | 0.527 | 0.460, 0.595 | | |
| SoC, health state 4 | 0.276 | 0.133, 0.419 | | |
| SoC, health state 5 | 0.067 | -0.029, 0.163 | | |
| SoC, health state 6 | 0.043 | -0.025, 0.110 | | |
| SoC, health state 7 | –0.333 | -0.398, -0.268 | | |
| SoC, health state 8 | –0.326 | -0.392, -0.259 | | |
| SoC, health state 9 | –0.359 | -0.460, -0.258 | | |
| **Adverse event disutility** | | | | |
| Pyrexia | –0.11 | Arbitrary ±20% | Section B.3.4.4 Page 145 | Estimates derived from the published literature |
| Hypersensitivity | –0.03 | Arbitrary ±20% | | |
| Headache | –0.12 | Arbitrary ±20% | | |
| Vomiting | –0.05 | Arbitrary ±20% | | |
| **Other disutility** | | | | |
| Vision loss utility multiplier | 87% | Arbitrary ±20% | Section B.3.4.5.1, Page 147 | The value of 0.87 was based on the quality of life associated with neovascular macular degeneration in the UK |
| **Caregiver disutility** | | | | |


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| State | Utility value: mean (standard error) | 95% CI | Reference in submission (section and page number) | Justification |
|---|---|---|---|---|
| Cerliponase alfa, health state 1 | –0.01 | Arbitrary ±20% | Section B.3.4.5.2, Page 147 | Derived from a report presenting challenges of living with and caring for a child affected by CLN2 and validated in an advisory board with clinical experts. |
| Cerliponase alfa, health state 2 | –0.01 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 3 | –0.01 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 4 | –0.03 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 5 | –0.04 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 6 | –0.05 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 7 | –0.07 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 8 | –0.08 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 9 | –0.09 | Arbitrary ±20% | | |
| SoC, health state 1 | –0.02 | Arbitrary ±20% | | |
| SoC, health state 2 | –0.025 | Arbitrary ±20% | | |
| SoC, health state 3 | –0.027 | Arbitrary ±20% | | |
| SoC, health state 4 | –0.054 | Arbitrary ±20% | | |
| SoC, health state 5 | –0.081 | Arbitrary ±20% | | |
| SoC, health state 6 | –0.108 | Arbitrary ±20% | | |
| SoC, health state 7 | –0.135 | Arbitrary ±20% | | |
| SoC, health state 8 | –0.162 | Arbitrary ±20% | | |
| SoC, health state 9 | –0.189 | Arbitrary ±20% | | |
| **Sibling disutility** | | | | |
| Cerliponase alfa, health state 1 | 0.00 | Arbitrary ±20% | Section B.3.4.5.2, Page 147 | Derived from a report presenting challenges of living with and caring for a child affected by CLN2 and validated in an advisory board with clinical experts. |
| Cerliponase alfa, health state 2 | 0.00 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 3 | –0.01 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 4 | –0.02 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 5 | –0.03 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 6 | –0.05 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 7 | –0.06 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 8 | –0.07 | Arbitrary ±20% | | |
| Cerliponase alfa, health state 9 | –0.08 | Arbitrary ±20% | | |
| SoC, health state 1 | 0.000 | Arbitrary ±20% | | |
| SoC, health state 2 | 0.000 | Arbitrary ±20% | | |


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| State | Utility value: mean (standard error) | 95% CI | Reference in submission (section and page number) | Justification |
|---|---|---|---|---|
| SoC, health state 3 | –0.023 | Arbitrary ±20% | | |
| SoC, health state 4 | –0.045 | Arbitrary ±20% | | |
| SoC, health state 5 | –0.068 | Arbitrary ±20% | | |
| SoC, health state 6 | –0.090 | Arbitrary ±20% | | |
| SoC, health state 7 | –0.113 | Arbitrary ±20% | | |
| SoC, health state 8 | –0.135 | Arbitrary ±20% | | |
| SoC, health state 9 | –0.158 | Arbitrary ±20% | | |

Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; DSU, decision support unit; EEPRU, Policy Research Unit in Economic Evaluation of Health and Care Interventions; NICE, National Institute for Health and Care Excellence; SoC, standard of care.


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## B.3.5. Cost and healthcare resource use identification, measurement

Methods and results of the SLR conducted as part of the appraisal for the identification of relevant cost and health care resource use data are presented in Appendix I.

### B.3.5.1. Intervention and comparators' costs and resource use

#### B.3.5.1.1. Acquisition costs

The list price of cerliponase alfa is £20,107 per 300 mg pack, consisting of two 150 mg vials.

[redacted]

In line with the SmPC, the drug dose and number of vials of cerliponase alfa required is modelled to be age-dependent (Table 61) (24).

**Table 61: Cerliponase alfa dosing**

| Age | Dose (mg) | Vials required |
|---|---|---|
| 0–6 months | 100 | 0.67 |
| 6 months to 1 year | 150 | 1 |
| 1 year to 2 years† | 284.62† | 1.90 |
| >2 years | 300 | 2 |

†200mg for the first 4 doses; 300mg for subsequent doses (assuming 22 subsequent doses).

Additionally, an adherence rate of 97.0% for cerliponase alfa, derived from the overall cohort in the MAA, was modelled to reflect real-world use and was consistent with the adherence rate from Study 190-201/202 (99.7%). A summary of the cost of cerliponase alfa is presented in Table 62.


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**Table 62: Cerliponase alfa cost**

| Treatment cost item | | Value | Source |
|---|---|---|---|
| Cost per 150 mg vial | | £10,053.50 | BioMarin Europe Ltd (equivalent to £20,107 per 300mg pack) |
| Number of vials required per dose | | 2 | Cerliponase alfa SmPC (24) |
| Adherence rate | | 97.0% | MAA (11) |
| Discount | [redacted] | [redacted] | Internal estimates |
| | [redacted] | [redacted] | |
| Cost per dose | [redacted] | [redacted] | – |
| | [redacted] | [redacted] | – |

Abbreviations: EAP, expanded access programme; MAA, managed access agreement; PAS, patient access scheme; SmPC, Summary of Product Characteristics.

As SoC was defined as established clinical management without cerliponase alfa, it was assumed to be associated with zero acquisition costs.

#### B.3.5.1.2. Administration costs

The costs associated with ICV device insertion and replacement were included for the cerliponase alfa arm. Costs were sourced from NHS reference costs 2021/22 (Table 63).

**Table 63: Cerliponase alfa administration costs**

| Cost element | Value | Source |
|---|---|---|
| One-off ICV insertion cost | £13,871.00 | NHS reference costs, 2021–22, AA50F, Very Complex Intracranial Procedures, 18 years and under, with CC Score 0–5, Elective (92) |
| Replacement ICV cost | £3,824.05 | NHS reference costs, 2021-22, AA57B, Minimal Intracranial Procedures, 18 years and under, Elective (92) |
| Time to replacement ICV (years) | 4 | Cerliponase alfa SmPC (24) |

Abbreviations: CC, complications and comorbidities; ICV, Intracerebroventricular; NHS, National Health Service.

#### B.3.5.1.3. Infusion costs

Treatment with cerliponase alfa is associated with a cost of hospital delivery. The cost was taken from the NHS reference costs 2021/22 (Table 64).

**Table 64: Infusion cost**

| Item | Value | Source |
|---|---|---|
| Cost per infusion | £875.11 | NHS reference costs, 2021–22, AA25G, Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC Score 0–4, Day Case |

Abbreviations: CC, complications and comorbidities; NHS, National Health Service.


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#### B.3.5.1.4. Cardiologist costs

### B.3.5.2. Health state unit costs and resource use

The cost of visits to healthcare professionals was considered by health state. Annual health state resource use frequencies were derived from clinical expert opinion during the 2016 Delphi panel (91). The mean values after three rounds of questions were used to inform the values for each health state. For the final two health states, excluding death, any changes from the health state 'ML score 0' were made due to advice from a palliative care specialist (39). Health state resource use was further validated in an advisory board, held with clinical experts, in November 2023 (42); clinical experts advised that ophthalmologist appointments should not be applied to SoC patients in any state, and critical care bed days should not be applied to SoC patients in health states 8 and 9.

For patients receiving treatment with cerliponase alfa, a CLN2 clinical expert advised that patients receiving treatment with cerliponase alfa attend an average of one annual cardiologist appointment per year.

Resource use estimates are presented for cerliponase alfa and SoC patients in Table 65 and Table 66, respectively. Costs were taken from the NHS reference costs 2021/22 or the Personal Social Services Research Unit (PSSRU) (92, 93) (Table 67).


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**Table 65: Health state resource use, cerliponase alfa**

| | Annual resource use frequency by health state | | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | |
| Specialist clinician | 1.6 | 1.6 | 2.7 | 2.7 | 2.7 | 3.2 | 3.2 | 3.2 | 3.2 | Delphi panel, December 2016 (91) and November 2023 advisory board (42) |
| Specialist nurse | 25.3 | 25.3 | 23.8 | 23.8 | 23.8 | 37.7 | 37.7 | 37.7 | 52.0 | |
| General practitioner | 2.8 | 2.8 | 5.0 | 5.0 | 5.0 | 17.3 | 17.3 | 17.3 | 17.3 | |
| Community paediatrician | 1.7 | 1.7 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | |
| Speech/Language therapists | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 1.7 | 1.7 | 1.7 | 1.7 | |
| Physiotherapist | 2.0 | 2.0 | 3.3 | 3.3 | 3.3 | 4.0 | 4.0 | 4.0 | 4.0 | |
| Family support worker | 1.8 | 1.8 | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | |
| Ophthalmologist | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.0 | 1.0 | 1.0 | 1.0 | |
| Health visitor | 0.7 | 0.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| Occupational therapist | 1.8 | 1.8 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | |
| Caregiver costs | 0.0 | 0.0 | 0.0 | 0.2 | 0.2 | 0.2 | 0.3 | 0.3 | 0.3 | |
| Critical care bed days | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.0 | 1.0 | 1.0 | 1.0 | |
| Hospitalisation costs | 0.0 | 0.0 | 0.0 | 2.0 | 2.0 | 2.0 | 0.0 | 0.0 | 0.0 | |
| Palliative Care | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 24.0 | 36.0 | 36.0 | |
| Educational support | 2.0 | 2.0 | 3.0 | 3.5 | 3.5 | 3.5 | 3.5 | 2.5 | 2.5 | |
| Cardiologist | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | CLN2 clinical expert advice |

**Table 66: Health state resource use, SoC**

| | Annual resource use frequency by health state | | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | |
| Specialist clinician | 1.6 | 1.6 | 2.7 | 2.7 | 2.7 | 3.2 | 3.2 | 3.2 | 3.2 | Delphi panel, December 2016 (91) and November 2023 advisory board (42) |
| Specialist nurse | 25.3 | 25.3 | 23.8 | 23.8 | 23.8 | 37.7 | 37.7 | 37.7 | 52.0 | |
| General practitioner | 2.8 | 2.8 | 5.0 | 5.0 | 5.0 | 17.3 | 17.3 | 17.3 | 17.3 | |
| Community paediatrician | 1.7 | 1.7 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | |
| Speech/Language therapists | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 1.7 | 1.7 | 1.7 | 1.7 | |
| Physiotherapist | 2.0 | 2.0 | 3.3 | 3.3 | 3.3 | 4.0 | 4.0 | 4.0 | 4.0 | |
| Family support worker | 1.8 | 1.8 | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | |


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| | Annual resource use frequency by health state | | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | |
| Ophthalmologist | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| Health visitor | 0.7 | 0.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| Occupational therapist | 1.8 | 1.8 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 | |
| Caregiver costs | 0.0 | 0.0 | 0.0 | 0.2 | 0.2 | 0.2 | 0.3 | 0.3 | 0.3 | |
| Critical care bed days | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.0 | 1.0 | 0.0 | 0.0 | |
| Hospitalisation costs | 0.0 | 0.0 | 0.0 | 2.0 | 2.0 | 2.0 | 0.0 | 0.0 | 0.0 | |
| Palliative Care | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 24.0 | 36.0 | 36.0 | |
| Educational support | 2.0 | 2.0 | 3.0 | 3.5 | 3.5 | 3.5 | 3.5 | 2.5 | 2.5 | |
| Cardiologist | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |

Abbreviation: SoC, standard of care.

**Table 67: Health state resource use costs**

| | Unit cost | | Reference | |
|---|---|---|---|---|
| | First attendance | Subsequent attendance | First attendance | Subsequent attendance |
| Specialist clinician† | £439.81 | £439.81 | NHS reference costs, 2021–22, WF01B, Non-Admitted Face-to-Face Attendance, First, Consultant-led, Paediatric Neuro-Disability (92) | NHS reference costs, 2021–22, WF01B, Non-Admitted Non-Face-to-Face Attendance, Follow-up, Consultant-led, Paediatric Neuro-Disability (92) |
| Specialist nurse‡ | £109.98 | £109.98 | NHS reference costs, 2021-22, N29CF, Other Specialist Nursing, Child, Face to face (92) | – |
| General practitioner | £41.00 | £41.00 | PSSRU 2022. Unit costs for a general practitioner, per surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualification costs (92) | – |
| Community paediatrician | £487.09 | £487.09 | NHS reference costs, 2021-22, WF01B, Non-Admitted Face-to-Face Attendance, First, Consultant-led, Community Paediatric Service (92) | NHS reference costs, 2021-22, WF01B, Non-Admitted Non-Face-to-Face Attendance, Follow-up, Consultant-led, Community Paediatric Service (92) |
| Speech/language therapists | £143.21 | £143.21 | NHS reference costs, 2021-22, A13C1, Speech and Language Therapist, Child, One to One (92) | – |
| Physiotherapist | £132.15 | £132.15 | NHS reference costs, 2021-22, A08C1,Physiotherapist, Child, One to One (92) | – |


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| | Unit cost | | Reference | |
|---|---|---|---|---|
| | First attendance | Subsequent attendance | First attendance | Subsequent attendance |
| Family support worker | £33.88 | £33.88 | PSSRU 2018. Family support worker, unit cost per hour. £31 inflated from 2018 prices to 2022 prices (92) | – |
| Ophthalmologist | £161.06 | £161.06 | NHS reference costs, 2021-22, WF01B, Non-Admitted Face-to-Face Attendance, First, Consultant-led, Paediatric Ophthalmology (92) | NHS reference costs, 2021-22, WF01B, Non-Admitted Non-Face-to-Face Attendance, Follow-up, Consultant-led, Paediatric Ophthalmology (92) |
| Health visitor | £94.25 | £94.25 | NHS reference costs, 2021-22, N03F, Health Visitor, Other Clinical Intervention (92) | – |
| Occupational therapist | £167.91 | £167.91 | NHS reference costs, 2021-22, A06C1, Occupational Therapist, Child, One to One (92) | – |
| Caregiver costs | £38,453.33 | £38,453.33 | NHS. Agenda for change – pay rates. Average of salaries for a band 6 nurse (<2 years' experience: £35,392; 2-5 years' experience: £37,350; 5+ years' experience: £42,618) (100) | – |
| Critical care bed days | £7,251.91 | £7,251.91 | NHS reference costs, 2021-22, XB01Z, Paediatric Critical Care, Advanced Critical Care 5 (Paediatric Intensive Care Unit) (92) | – |
| Hospitalisation costs | £3,702.95 | £3,702.95 | NHS reference costs, 2021-22, XB02Z, Paediatric Critical Care, Advanced Critical Care 4 (Paediatric Intensive Care Unit) (92) | – |
| Palliative care | £167.30 | £167.30 | NHS reference costs, 2021-22, N21CF, Specialist Nursing, Palliative/Respite Care, Child, Face to face (92) | – |
| Educational support | £1,643.31 | £1,643.31 | PSSRU 2017. Education support, children aged 4-11 with low functioning autism living in private households with family. £1,485 inflated from 2017 prices to 2022 prices (93) | – |
| Cardiologist | £169.39 | £169.39 | NHS reference costs, 2021-22, Total outpatient attendances, service code 320, Cardiology Service (92) | – |

†Includes: neurologists, respiratory consultants, etc.; ‡Includes epilepsy nurse, nurse specialist, community nurse, etc.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.


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### B.3.5.3. Adverse reaction unit costs and resource use

Adverse reaction costs were derived from NHS reference costs 2021/22 and are presented in Table 68.

**Table 68: AE costs**

| AE | Cost per event | Reference |
|---|---|---|
| Pyrexia | £882.69 | NHS reference costs, 2021-22, PW20C, Paediatric Fever of Unknown Origin with CC Score 0. (92) |
| Hypersensitivity | £593.61 | NHS reference costs, 2021-22, PJ66C, Paediatric, Rash or Other Non-Specific Skin Eruption with CC Score 0. (92) |
| Headache | £708.13 | NHS reference costs, 2021-22, PR04C, Paediatric, Headaches or Migraines with CC Score 0. (92) |
| Vomiting | £785.03 | NHS reference costs, 2021-22, PF28E, Paediatric, Feeding Difficulties or Vomiting with CC score 0. (92) |

Abbreviations: AE, adverse event; CC, complications and comorbidities.

### B.3.5.4. Miscellaneous units – Costs and resource use

#### B.3.5.4.1. Progressive symptom costs

**Distress**

For patients with distress, drugs associated with distress management were modelled. The list of medications was derived from Williams et al, 2017 and used to calculate annual medication costs (15). It was assumed an even distribution of distress medications were used in the absence of medication details from patient narratives (Table 69).

**Table 69: Distress medication usage**

| | Proportion of distress medication usage |
|---|---|
| Acetaminophen | 14% |
| Methadone | 14% |
| Morphine | 14% |
| Hydromorphone | 14% |
| Amitriptyline | 14% |
| Gabapentin | 14% |
| Pregabalin | 14% |

Dosing of distress medications were derived from the British National Formulary (BNF) and unit costs were derived from the drugs and pharmaceutical electronic market information tool (eMIT), where possible, and the BNF (Table 70) (101, 102).


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**Table 70: Distress medication costs**

| | Daily dose | mg per unit | Units per pack | Cost per pack | Reference |
|---|---|---|---|---|---|
| Acetaminophen | 4000 | 500 | 100 | £0.88 | eMIT (101) |
| Methadone | 15 | 5 | 50 | £6.27 | |
| Morphine | 1.2 | 100 | 1 | £5.60 | |
| Hydromorphone | 7.8 | 1.3 | 56 | £8.82 | BNF (102) |
| Amitriptyline | 10 | 25 | 28 | £0.29 | eMIT (101) |
| Gabapentin | 2.25 | 400 | 100 | £1.82 | |
| Pregabalin | 375 | 25 | 56 | £0.96 | |

Abbreviations: BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool.

### Dystonia

Drugs associated with the management of dystonia were considered. The list of medications was derived from Williams et al, 2017 and used to calculate annual medication costs (15). To avoid the possibility of double counting the anti-epileptic drugs (AED) clonazepam and clobazam, it was assumed patients with dystonia were already receiving AEDs. It was assumed that an even distribution of dystonia medications was used in the absence of medication details from patient narratives (Table 71).

**Table 71: Dystonia medication usage**

| | Proportion of dystonia medication usage |
|---|---|
| Baclofen | 33.3% |
| Clonidine | 33.3% |
| Trihexyphenidyl | 33.3% |

Dosing of dystonia medications were derived from the BNF and unit costs were derived from eMIT (Table 72) (101, 102).

**Table 72: Dystonia medication costs**

| | Daily dose | mg per unit | Units per pack | Cost per pack | Reference |
|---|---|---|---|---|---|
| Baclofen | 1.38 | 10 | 84 | £0.91 | eMIT (101) |
| Clonidine | 0.025 | 0.025 | 112 | £10.43 | |
| Trihexyphenidyl | 2 | 5 | 84 | £3.23 | |

Abbreviations: eMIT, Drugs and pharmaceutical electronic market information tool.

### Myoclonus

Drugs associated with the management of myoclonus were modelled. The list of medications was derived from Williams et al, 2017 and used to calculate annual medication costs (15). To avoid double counting the cost the AEDs, it was assumed patients with dystonia were already receiving AEDs. Therefore, only phenobarbital was modelled for myoclonus.


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Dosing of myoclonus medications was derived from the BNF and unit costs were derived from eMIT (Table 73) (101, 102).

**Table 73: Myoclonus medication costs**

| | Daily dose | mg per unit | Units per pack | Cost per pack | Reference |
|---|---|---|---|---|---|
| Phenobarbital | 5.25 | 200 | 10 | £107.39 | eMIT (101) |

Abbreviations: eMIT, Drugs and pharmaceutical electronic market information tool.

### Musculoskeletal pain

It is anticipated the medications used for musculoskeletal pain are the same as those used to treat other progressive symptoms. No additional costs have therefore been modelled.

### Feeding tube

Costs associated with the replacement of a feeding tube were modelled by treatment arm. Costs associated with feeding tube insertion have not been modelled as it is anticipated that all patients will require feeding tube insertion during their lifetime, and therefore no difference in cost is anticipated between the cerliponase alfa and SoC arms.

The proportion of patients requiring a feeding tube, by health state, was derived from clinical expert opinion (Table 74) (42). Clinical experts at GOSH suggested common practice would be to replace the feeding tube once every two years.

**Table 74: Proportion of patients requiring feeding tube by health state**

| Health state | Proportion requiring feeding tube | |
|---|---|---|
| | Cerliponase alfa | SoC |
| 1 | 0% | 0% |
| 2 | 0% | 10% |
| 3 | 0% | 50% |
| 4 | 0% | 70% |
| 5 | 20% | 100% |
| 6 | 80% | 100% |
| 7 | 100% | 100% |
| 8 | 100% | 100% |
| 9 | 100% | 100% |

Abbreviation: SoC, standard of care.

The cost of feeding tube replacement was derived from the NHS reference costs and is presented in Table 75.


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**Table 75: Feeding tube costs**

| Parameter | Value | Reference |
|---|---|---|
| Annual feeding tube replacement cost | £676.92 | Assumed to apply every 2 years. £1,353.84/2 = £676.92. NHS reference costs, 2021-22, FE23C, Endoscopic or Intermediate, Upper Gastrointestinal Tract Procedures, between 5 and 18 years (92) |

Abbreviations: NHS, National Health Service.

### Seizures

Patient narratives from studies 190-201/202 were used to inform the proportion experiencing seizures by treatment arm which suggested all patients required AEDs (94).

The cost of AEDs was considered for patients experiencing seizures. The types of medication and their distribution were taken from patient narratives in Studies 190-202 (Table 76).

**Table 76: AED medication usage**

| | Proportion of AED usage |
|---|---|
| Sodium valproate (Vl) | 17% |
| Lamotrigine (Lm) | 0% |
| Levetiracetam (Lv) | 4% |
| Topiramate (Tp) | 0% |
| Clobazam (Cb) | 0% |
| Zonisamide (Zn) | 0% |
| Clonazepam (Cn) | 0% |
| Vl + Lv | 17% |
| Vl + Lv + Zn | 4% |
| Vl + Lv + Cn | 9% |
| Vl + Lv + Lm | 4% |
| Vl + Lm + Zn | 4% |
| Vl + Lm + Cb | 9% |
| Vl + Lm + Tp | 4% |
| Vl + Zn + Cb | 13% |
| Vl + Cn + Tp | 4% |
| Lv + Zn + Cb | 4% |
| Lv + Lm + Tp | 4% |

Abbreviations: AED, anti-epileptic drug; Cb, clobazam; Cn, clonazepam; LM, lamotrigine; LV, levetiracetam; Tp, topiramate; Vl, sodium valproate; Zn, zonisamide.

Dosing of medications were derived from the BNF and unit costs were derived from eMIT (Table 77) (101, 102).


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**Table 77: AED costs**

| | Daily dose (mg/kg) | mg per unit | Units per pack | Cost per pack | Reference |
|---|---|---|---|---|---|
| Topiramate | 7 | 25 | 60 | £7.58 | eMIT (101) |
| Clobazam | 0.65 | 500 | 1 | £19.83 | |
| Clonazepam | 4.5 | 2 | 105 | £15.82 | |
| Lamotrigine | 3 | 25 | 56 | £2.47 | BNF (102) |
| Levetiracetam | 15 | 250 | 60 | £1.97 | |
| Sodium valproate | 27.5 | 400 | 5 | £12.66 | eMIT (101) |
| Zonisamide | 7 | 52 | 14 | £1.08 | |

Abbreviations: AED, anti-epileptic drug; eMIT, Drugs and pharmaceutical electronic market information tool.

Despite patients with seizures receiving treatment with AEDs, clinical experts were of the opinion that patients with CLN2 disease would still experience chronic seizures. The cost of these seizures was modelled as being dependent on the number of seizures experienced annually. For each modelled seizure, rescue medications and hospitalisation costs were applied. The types of medications used and the proportion resulting in hospitalisation were derived from patient narratives in Study 190-201/202 (Table 78).

**Table 78: Rescue medication use**

| | Rescue medication incidents (per year) | Proportion of patients receiving drug |
|---|---|---|
| Rectal diazepam | 1.26 | 48.9% |
| Intravenous lorazepam | 1.06 | 40.9% |
| Buccal midazolam | 0.15 | 5.8% |
| Intravenous phenobarbital | 0.11 | 4.4% |
| **Total** | **2.59** | **100%** |

To derive a weighted cost of seizure, dosing of medications was derived from the BNF and unit costs were derived from eMIT and the BNF (Table 79) (101, 102).

**Table 79: Rescue medication costs**

| | Daily dose | mg per unit | Units per pack | Cost per pack | Reference |
|---|---|---|---|---|---|
| Rectal diazepam | 10 | 5 | 5 | £2.50 | eMIT (101) |
| Intravenous lorazepam | 4 | 4 | 10 | £82.99 | |
| Buccal midazolam | 7.5 | 50 | 10 | £6.72 | |
| Intravenous phenobarbital | 200 | 30 | 10 | £144.40 | BNF (102) |

Abbreviations: BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool.


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#### B.3.5.4.2. Cost of vision loss

An annual cost of blindness was applied to:

- All patients in Health states 7-9
- A proportion of patients in health states 1–6, rising from 0% at age 6 to 100% at age 20.

Costs were derived from Lotery et al, 2007 and inflated to 2022 values using the Hospital and Community Health Services (HCHS) inflation index published by the PSSRU (93, 99). The cost associated with vision loss is presented in Table 80.

**Table 80: Cost of vision loss**

| | | AMD | Control | Difference |
|---|---|---|---|---|
| Direct vision-related medical cost | | £1,553.14 | £44.76 | £1,508.38 |
| Direct non-vision-related medical cost | | £431.01 | £412.72 | £18.29 |
| Direct non-medical related cost | | £1,839.74 | £59.57 | £1,780.17 |
| Total difference (annual cost of vision loss) | Original 2005 | – | – | £3,306.84 |
| | Inflated to 2022 (index 1.38) | – | – | £4,561.74 |

Abbreviations: AMD, age-related macular degeneration.

#### B.3.5.4.3. Residential care costs

It is expected that a proportion of adult patients with CLN2 will require residential care (Table 81).

**Table 81: Residential care costs**

| | Value | Reference |
|---|---|---|
| Care package cost per year | £49,359 | PSSRU. Unit Costs of Health & Social Care 2017. £44,604 per year. Inflated to 2021-22 prices using PSSRU 2022 (93) |

Abbreviations: PSSRU, Personal Social Services Research Unit.

A report by the Centre for Disability Research (CeDR) presented accommodation arrangements for people with mild/moderate, severe, and profound multiple learning disabilities (Table 82) (103).

**Table 82: Accommodation arrangements for people with learning disabilities, CeDR (103)**

| | Mild or moderate | Severe | Profound multiple |
|---|---|---|---|
| Private households (total) | 74% | 74% | 65% |
| Other accommodations | 26% | 26% | 35% |

Abbreviations: CeDR, Centre for Disability Research.


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In the absence of data for patients with CLN2, it was assumed patients with ML score (Table 83):

- 6 and 5 have no learning disabilities
- 4 and 3 have mild/moderate learning disabilities
- 2 and 1 have severe learning disabilities
- 0 have profound multiple learning disabilities.

**Table 83: Residential care proportions**

| Health state | Proportion entering NHS/Social Care funded accommodation |
|---|---|
| 1 | 0% |
| 2 | 0% |
| 3 | 26% |
| 4 | 26% |
| 5 | 26% |
| 6 | 26% |
| 7 | 35% |
| 8 | 35% |
| 9 | 35% |

Abbreviations: NHS, National Health Service.

#### B.3.5.4.4. Psychiatric/behavioural support costs

The cost of psychiatric/behavioural support was included in the decision-making model in the original appraisal. For this reappraisal, clinicians were asked to validate psychiatric/behavioural support costing assumptions in a November 2023 clinical advisory board (42). Both clinical experts agreed that patients do attend special educational needs (SEN) school but these do not constitute psychiatric/behavioural support and do not reflect a need for such support. In addition, advisers agreed that there is no evidence from patients treated with cerliponase alfa to indicate such support would be required in the future. Therefore, cost of psychiatric/behavioural support has not been included in the updated analysis.

#### B.3.5.4.5. Diagnostic testing costs

Diagnostic testing costs have not been included in the analysis, as all patients with CLN2 disease are expected to receive a diagnosis. The availability of cerliponase alfa may result in diagnostic testing happening at an earlier stage of disease, but this would not result in any additional costs.


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## B.3.6. Uncertainty

As CLN2 disease is an ultra-rare condition, and similarly for all treatments for small populations, evidence generation for cerliponase alfa is challenging. For this appraisal, evidence has been derived from the best available sources, including CLN2 disease clinical expert opinion; however, assumptions have been made due to the paucity of data. Sensitivity analyses have been undertaken to test structural and parameter uncertainty (Section B.3.10). In addition, assumptions and inputs have been validated by clinical experts where possible.

## B.3.7. Managed access proposal

Not applicable.

## B.3.8. Summary of base-case analysis inputs and assumptions

### B.3.8.1. Summary of base-case analysis inputs

A summary of the base case analysis input parameters is provided in Table 84.


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**Table 84: Summary of variables applied in the economic model**

| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| **Patient characteristics** | | | |
| Percentage female (%) | 50% | Fixed | Section B.3.2.1 |
| Starting distribution | Table 41 | Fixed | Section B.3.3.1 |
| Age (years) | Table 40 | Fixed | |
| **Clinical data** | | | |
| Transitions | | | Section B.3.3.2 |
| Transition intensities, health states 1–7 | Table 42 and Table 43 | Log-normal | |
| Time to transition, health states 7–9 | Table 44 | Log-normal | |
| Proportion with vision loss | – | Fixed | Section B.3.3.4 |
| Vision loss and progressive symptoms | | | Section B.3.3.3 |
| Proportion with distress | Table 45 | Beta | |
| Proportion with dystonia | Table 47 | Beta | |
| Proportion with myoclonus | Table 48 | Beta | |
| Proportion requiring feeding tube | Table 50 | Beta | |
| Proportion with musculoskeletal pain | Table 49 | Beta | |
| Overall number of seizures | Table 46 | Gamma | |
| Number of seizures requiring rescue medication | Table 46 | Gamma | |
| Frequency of AEs (cerliponase alfa) | Table 51 | Beta | Section B.3.3.5 |
| Infusion-related mortality (cerliponase alfa) | 0.00% | Beta | Section B.3.3.6 |
| **Utility data** | | | |
| Health state utility values | Table 52 | Beta | Section B.3.4.2.1 |
| Vision loss utility multiplier | – | Beta | Section B.3.4.5.1 |
| Adverse event disutility | Table 54 | Beta | Section B.3.4.4 |
| Caregiver disutility | | | Section B.3.4.5.2 |
| Number of family caregivers | Table 55 | Gamma | |
| Caregiver disutility | Table 57 | Beta | |
| Sibling disutility | | | Section B.3.4.5.2 |
| Average number of siblings per CLN2 patient | 0.94 | Gamma | |


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| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Sibling disutility | Table 59 | Beta | |
| **Cost data** | | | |
| Cerliponase alfa acquisition costs | Table 62 | Fixed | Section B.3.5.1.1 |
| Cerliponase alfa administration costs | Table 63 | Gamma | Section B.3.5.1.2 |
| Cerliponase alfa infusion costs | Table 64 | Gamma | Section B.3.5.1.3 |
| Health state resource use | | | Section B.3.5.2 |
| Resource use | Table 65 | Gamma | |
| Health state resource use costs | Table 67 | Gamma | |
| Adverse event costs | Table 68 | Gamma | Section B.3.5.3 |
| Progressive symptom costs | | | Section B.3.5.4.1 |
| Distress medication usage | Table 69 | Beta | |
| Distress medication costs | Table 70 | Fixed | |
| Dystonia medication usage | Table 71 | Beta | |
| Dystonia medication costs | Table 72 | Fixed | |
| Myoclonus medication usage | – | Beta | |
| Myoclonus medication costs | Table 73 | Fixed | |
| Musculoskeletal pain medication usage | – | Beta | |
| Musculoskeletal pain medication costs | – | Fixed | |
| Proportion of patients requiring a feeding tube | Table 74 | Beta | |
| Feeding tube costs | Table 75 | Gamma | |
| AED medication usage | Table 76 | Beta | |
| AED costs | Table 77 | Fixed | |
| Rescue medication usage | Table 78 | Beta | |
| Rescue medication costs | Table 79 | Fixed | |
| Cost of vision loss | Table 80 | Gamma | Section B.3.5.4.2 |
| Proportion requiring residential care | Table 83 | Beta | Section B.3.5.4.3 |
| Residential care costs | Table 81 | Gamma | |

Abbreviations: AE, adverse event; AED, anti-epileptic drug; CLN2, neuronal ceroid lipofuscinosis type 2; SoC, standard of care.


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### B.3.8.2. Assumptions

Assumptions used in the economic model are presented in Table 85.

**Table 85: Model assumptions**

| | Assumption | Justification |
|---|---|---|
| Patient population | The population was assumed to be 50% male and 50% female | During the 2016 Delphi panel, workshop 3, clinical experts considered that there was no difference in CLN2 prevalence by sex (91) |
| | The distribution of patients across health states at model entry was derived from patients aged less than 3 years at the start of Study 190-203 | Patients aged less than 3 years in Study 190-203 are expected to reflect a realistic distribution of patients in the near future, with a shift towards younger patients with improved ML scores at baseline following increased awareness of CLN2 disease.<br><br>Scenario analyses consider alternative baseline health state distributions. |
| Transitions between health states | Cerliponase alfa patients in health state 1 (ML score of 6) at baseline are assumed to remain in this state for the first 6 years of the model | This is in line with the observed data for patients aged less than 3 years in Study 190-203. |
| | After the first 6 years, patients in health state 1 (ML score of 6) are assumed to transition at half the rate observed for patients in other starting states | This assumption has been made in the absence of other data; clinical expert feedback advised that this assumption may be conservative, given that these patients were not observed to decline over the 6-year study period. Scenario analyses consider alternative reductions to the transition rate. |
| | Time to complete vision loss (52 weeks) from reaching an ML score of 0, i.e. transition between health state 7 and health state 8, is the same for both cerliponase alfa and SoC arms in the model. | Data were not available for these transitions, as no patients progressed beyond an ML score of 0 in the clinical trial programmes and the MAA cohort, and no information was available in the natural history data on the time to vision loss or time to requirement of palliative care.<br><br>Therefore, clinical expert opinion was sought in the 2016 Delphi panel where experts estimated the time of these transitions for the SoC arm (91).<br><br>In the absence of equivalent estimates for patients receiving cerliponase alfa, a conservative assumption was adopted to assume equal SoC arm transitions. However, as cerliponase alfa treatment has been shown to slow disease progression, treatment is likely to increase the time between these transitions |
| | Time from complete vision loss to requiring palliative care (52 weeks), i.e. transition between health state 8 and health state 9, was assumed to be the same for both cerliponase alfa and standard care arms in the model | |
| | Time receiving palliative care before disease-related mortality (52 weeks) was assumed to be the same for both cerliponase alfa and standard care arms in the model | |
| Treatment of seizures | All patients receive AEDs | Patient narratives from studies 190-201/202 indicated that all patients received at least one AED |
| | All patients requiring medication for myoclonus were already receiving treatment with AEDs | This was assumed in the absence of data regarding medications for the management of myoclonus in CLN2. To avoid the possibility of double counting |


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| | Assumption | Justification |
|---|---|---|
| | | AEDs, all patients were assumed to received AEDs, therefore the phenobarbital was the only additional medication costed for the treatment of myoclonus |
| | Hospitalisation cost for chronic seizures is applied only to the proportion of rescue medication delivered intravenously | Data on which seizures required hospital admission for patients were not available, so it was assumed that if intravenous rescue medication was required, then a hospitalisation cost would need to be applied. Information on the proportion of rescue medications provided intravenously was taken from the patient narratives |
| Other progressive symptoms | Proportion of patients experiencing progressive symptoms (seizures, reported distress, dystonia, myoclonus, musculoskeletal pain, and the requirement of a feeding tube) in each health state differ between arms. | Clinical expert opinion in a series of advisory boards, held in 2023, suggested the proportion of patients experiencing the progressive symptoms: distress, seizures, dystonia, myoclonus, musculoskeletal pain, and the requirement of a feeding tube differs by health state and treatment arm (cerliponase alfa and SoC) (39, 42). Proportions of progressive events are expected to be lower for milder health states and lower for patients receiving treatment with cerliponase alfa. |
| | The number of appointments relating to progressive symptoms in health state 9 was assumed equal to health state 8, with the exception of appointments associated with palliative care, which were informed by separate expert opinion | Data on the categories of appointments received by patients in health state 8 were derived from the Delphi panel, however, equivalent data for health state 9 were not collected. An equal number of appointments between states 8 and 9 was assumed (excluding those associated with palliative care) due to the similarities between these states |
| | Feeding tubes were assumed to require replacement every two years | This was assumed in line with usual practice at GOSH (104) |
| | It was assumed that the proportions of patients using the different reported distress medications recommended in the literature are equal across the different types of medication. | There were no data available on which medications are most commonly used when treating reported distress in CLN2 patients, thus it was assumed that all recommended medications are equally likely to be administered. |
| | It was assumed that the proportion of patients using the different dystonia medications is equal across all recommended medications, and that all patients with dystonia are already receiving AEDs (to avoid double-counting clonazepam and clobazam costs) | There are no data available on which medications are most commonly used when treating dystonia in CLN2 patients. All patients are modelled as receiving AEDs, so it could be assumed that all patients with dystonia would be receiving AEDs |
| Administration of cerliponase alfa | The adherence rate used in the model (97.0%) derived from the MAA, was assumed to be constant throughout the model time horizon | In line with the source of the distribution of patients across health states at model entry, the adherence rate from the MAA data was selected to reflect cerliponase alfa adherence in UK clinical practice. Moreover, the MAA adherence rate is consistent with the trial (99.74%). |
| | Patients stop receiving cerliponase alfa treatment when they reach health state 6 (ML score of 1). Upon discontinuing cerliponase alfa, patients switch to transition probabilities and utility values observed in the SoC arm | Discontinuation at a ML score of 1 was assumed as it is anticipated that patients have progressed such that continued treatment with cerliponase alfa is unlikely to improve motor and language capabilities. |
| | The rate of cerliponase alfa related AEs was assumed to be constant through the model time horizon | There are no data available on how the rate of cerliponase alfa related AEs changes over time beyond the trial, so the rate of adverse reactions that was observed during |


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| | Assumption | Justification |
|---|---|---|
| | | the trial was assumed to stay the same, in line with the dosing schedule of cerliponase alfa being unchanged throughout the model time horizon |
| | Additional mortality associated with infections from ICV treatment was assumed to be zero | No data were available in the literature, and no deaths due to infections occurred in Study 190-201/202, so this was thought to be an acceptable assumption to make in the absence of further information. |
| AEs | Hypersensitivity, headaches, and vomiting were assumed to last for one day, when calculating the disutility due to AEs | No data were available for how long patients experienced these AEs in studies 190-201 and 190-202, thus it was assumed that each event would last for one day based on the expected severity of these AEs |
| | No treatment related AEs were applied to the SoC arm of the model | In the SoC arm of the model, patients do not receive the treatment (cerliponase alfa) and thus no treatment related AEs are applied to these patients |
| | Additional mortality from AEs was not considered | No deaths due to AEs occurred in Study 190-201/190-202, so this was considered to be an acceptable assumption to make in the absence of further information |
| Caregiver costs and disutilities | Caregiver disutility is only applied to the proportion of care provided by family caregivers. | It is assumed that care only has an impact on the quality of life of family caregivers and does not impact non-family caregivers, e.g. community nurses. |
| | Caregiver disutility assumed to increase linearly after the first two health states, with the values for health states 1 and 2 being provided by clinical experts, for 30 years. | The burden on each carer is lower in the first two health states, and according to clinical experts increases as the disease progresses. Clinical experts provided the disutility values for the first two health states, in the absence of data (23). |
| | Caregiver costs are only applied to the proportion of care not provided by family caregivers | Family caregivers do not receive payment for the care they provide, whereas non-family caregivers, such as community nurses, are paid for by the NHS. Therefore, costs were applied to the proportion of care provided by non-family caregivers only |
| Sibling disutilities | Sibling disutility was not applied in the first two health states and was then assumed to increase linearly across the remaining health states, for 30 years | The burden on siblings is lower in the first two health states and increases as disease severity for the affected sibling increases, according to clinical experts (23). This can be due to the increased caregiving demands on parents' time, the involvement of siblings in caregiving, and the emotional impact of the rapid decline in their sibling |
| | Sibling disutility remains the same across the time horizon | No data on how child sibling disutility changes over time were available |

Abbreviations: AE, adverse event; AED, anti-epileptic drug; CLN2: neuronal ceroid lipofuscinosis type 2; GOSH, Great Ormond Street Hospital; ICV: intracerebroventricular; MAA, managed access agreement; NHS, National Health Service; SoC, standard of care.


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## B.3.9. Base-case results

### B.3.9.1. Base-case incremental cost-effectiveness analysis results

Base-case results for cerliponase alfa versus SoC are presented in Table 86 and consider all discounts outlined in Table 62 for cerliponase alfa. Cerliponase alfa is associated with a discounted life year (LY) and quality-adjusted of life year (QALY) gain of 17.41 and 17.35 respectively, and an undiscounted QALY gain of 36.25.

**Table 86: Base-case results (deterministic) – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | 5.37 | -0.28 | - | - | - | - | - |
| Cerliponase alfa | [redacted] | 22.78 | 17.07 | [redacted] | 17.41 | 17.35 | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 87: Net health benefit – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | NHB at £300,000 |
|---|---|---|---|---|---|
| SoC | [redacted] | -0.28 | - | - | - |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; SoC, standard of care.


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## B.3.10. Exploring uncertainty

### B.3.10.1. Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

Results of the PSA comparison vs SoC are presented in Table 88. The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were 17.78, resulting in a probabilistic ICER of [redacted]. The results were congruent with the deterministic incremental costs of [redacted] and incremental QALYs of 17.35.

**Table 88: Probabilistic sensitivity analysis results – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| SoC | [redacted] | -0.17 | - | - | - |
| Cerliponase alfa | [redacted] | 17.61 | [redacted] | 17.78 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

The CEP and CEAC are presented in Figure 19 and Figure 20, respectively.

**Figure 19: Cost-effectiveness plane (cerliponase alfa vs SoC)**



Abbreviations: QALYs, quality-adjusted life years; SoC, standard of care.


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**Figure 20: Cost-effectiveness acceptability curve (cerliponase alfa vs SoC)**



Abbreviations: SoC, standard of care.

### B.3.10.2. Deterministic sensitivity analysis

The results of deterministic sensitivity analysis vs SoC are presented in Table 89, and a tornado diagram of deterministic results is presented in Figure 21. Parameters were varied using 95% confidence intervals where possible, or ±20% of the mean value. The most influential parameters were those associated with transitions in the cerliponase alfa arm and vision loss utility multiplier.

**Table 89: Deterministic sensitivity analysis results**

| Parameter | ICER at lower value of parameter | ICER at upper value of parameter |
|---|---|---|
| Transition intensity, cerliponase alfa, Study 190-203, 1 to 2 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 5 to 6 | [redacted] | [redacted] |
| Vision loss utility multiplier | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 2 to 1 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 2 to 3 | [redacted] | [redacted] |
| Transition intensity, SoC, Study 190-203, 1 to 2 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, all patients, 6 to 7 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 3 to 2 | [redacted] | [redacted] |
| Transition intensity, SoC, Study 190-203, 2 to 3 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, all patients, 6 to 5 | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio.


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**Figure 21: Tornado diagram**



Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care.

### B.3.10.3. Scenario analysis

Scenario analyses were performed to explore the impact of varying key structural assumptions on results. A summary of considered scenario analyses is presented in Table 90.

**Table 90: Scenario analysis assumptions**

| Scenario | Scenario assumptions | Base-case assumptions |
|---|---|---|
| Cerliponase alfa treatment discontinuation | • Discontinuation at health state 7 (ML score 0)<br>• No discontinuation | Treatment discontinuation at health state 6 (ML score 1) |
| Source of age and health state distribution at baseline | • All patients in Study 190-203<br>• New patients in the MAA | Starting age and distribution derived from patients <3 years in Study 190-203. |
| Source of transition probabilities | • All patients†<br>• All patients (piecewise at 6 months) † | Transition probabilities derived from patients <3 years in Study 190-203. |
| Duration of initial stabilisation for patients with a baseline ML score of 6 | 12 years | 6 years |
| Transition probability risk reduction for cerliponase alfa stabilisers | • 75%<br>• 100% | 50% |
| Source of health state utility values | The MAA | Gissen 2021 |

†Note all patients include patients receiving cerliponase alfa in Study 190-201/202, Study 190-203, and the MAA.
Abbreviations: MAA, managed access agreement; ML, motor language.

The results of the scenario analyses are presented in Table 91.


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**Table 91: Scenario analysis results**

| Scenario | Incremental costs | Incremental QALYs | ICER (£/QALY) | % change from base case ICER |
|---|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] | [redacted] |
| Treatment discontinuation at health state 7 (ML score 0) | [redacted] | 17.79 | [redacted] | [redacted] |
| No treatment discontinuation | [redacted] | 17.86 | [redacted] | [redacted] |
| Starting distribution: Study 190-203 | [redacted] | 11.78 | [redacted] | [redacted] |
| Starting distribution: MAA (new patients) | [redacted] | 7.82 | [redacted] | [redacted] |
| Source of transitions: All patients | [redacted] | 14.27 | [redacted] | [redacted] |
| Source of transitions: All patients (piecewise at 6 months) | [redacted] | 22.86 | [redacted] | [redacted] |
| Duration of ML 6 stabilisation: 12 years | [redacted] | 18.52 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 75% | [redacted] | 19.54 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 100% | [redacted] | 22.11 | [redacted] | [redacted] |
| Source of utility values: MAA | [redacted] | 16.20 | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

## B.3.11. Subgroup analysis

No subgroup analysis was performed.

## B.3.12. Benefits not captured in the QALY calculation

CLN2 is associated with significant impact on patients and their families, which has been captured in the economic analysis wherever possible. However, the full benefit of access to and treatment with cerliponase alfa for patients with CLN2 disease cannot be captured using the QALY alone.

Cerliponase alfa is the first and only treatment for patients with CLN2 disease. In the absence of cerliponase alfa, patients receive treatments to relieve the symptoms of the condition only and can experience rapid disease progression involving worsening of symptoms such as changes in vision, language, mobility, and increased frequency and severity of seizures.

CLN2 patient advocates agreed that the day-to-care care burden is extensive, with some patients requiring 24/7 all-round care. Advocates highlighted the financial implications of care for patients with CLN2 disease including disruption to work (productivity loss) and additional personal financial implications. The impact of the financial burden on families


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cannot be adequately captured in the reference case analysis. However, the impact of cerliponase alfa in slowing disease progression can aid the alleviation of the financial complications for families of patients with CLN2 as the need for substantial changes to care decreases.

In addition, patient advocates agreed that the impact on siblings of patients with CLN2 is profound. Siblings were reported to experience major anxieties and substantial psychological impact. As siblings grow up during their affected siblings' deterioration, their awareness of the disease increases, with a patient advocate reporting the development of post-traumatic stress disorder as a result. The deep impact of CLN2 for an unaffected sibling may last a lifetime, the impact of which can only be naively estimated.

### B.3.13. Validation

Internal validation of the economic model was performed by the model developers and by a health economist not involved in the development of the model.

In addition, key modelling assumptions were validated by clinical experts to ensure the model was reflective of clinical practice. For this reappraisal, a series of advisory boards were conducted in 2023, including two held with CLN2 clinical experts. Key modelling inputs discussed with experts included:

- Clinical data
    - Proportion of patients experiencing progressive symptoms (distress, dystonia, myoclonus, musculoskeletal pain, seizures, and the requirement of a feeding tube) in each health state by treatment arm
- Utility data
    - Health state vignettes
    - Family caregiver and sibling disutility
- Cost data
    - Included cost types
    - Medical resource use by treatment arm
    - Requirement for psychiatric/behavioural support
    - Requirement for residential care.

It was not possible to perform external validation due to the rarity of CLN2 and the lack of available treatment options.


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## B.3.14. Interpretation and conclusions of economic evidence

Based on the discounted price of cerliponase alfa, this cost-effectiveness analysis estimates cerliponase alfa to be associated with a QALY gain of 17.35 and an incremental cost of [redacted] resulting in an ICER of [redacted] per QALY gained versus SoC and a base case undiscounted QALY gain of 36.25. Extensive sensitivity and scenario analyses show that the base-case ICER is generally robust to alternative assumptions, and the results are broadly consistent with those presented in HST12.

The key strengths of the analysis are:

- The analysis has been conducted in line with the NICE reference case
- Whenever appropriate, trial data, MAA data, or natural history data were used to inform the model
- Where inputs could not be sourced from the literature, trial or MAA data, multiple clinical experts were consulted to source these inputs
- Where possible, the inputs, assumptions and results were validated by clinical experts with expertise in CLN2 disease and cerliponase alfa, in order to reliably reflect UK clinical practice
- The analysis may be considered conservative as it does not account for the possibility of newborn screening in the near future.

A limitation of this analysis is that there was no head-to-head trial data directly comparing outcomes for patients treated with cerliponase alfa vs SoC. Transition probabilities for health states 7–9 were also derived from a Delphi panel in the absence of alternative evidence. However, given that these transition probabilities were assumed to be equivalent for cerliponase alfa and SoC, the impact is considered conservative.

The results of the analysis have identified that cerliponase alfa provides substantial QALY gain vs SoC.

## B.3.15. Cost to the NHS and Personal Social Services

### B.3.15.1. Eligible population

The population considered eligible for treatment with cerliponase alfa is people with CLN2 disease.


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The number of patients currently receiving cerliponase alfa is 33, and one patient has previously declined treatment with cerliponase alfa; the prevalent eligible population is therefore estimated to be 34. Parameters used to estimate the incident eligible population in England are summarised in Table 92.

**Table 92: Parameters used to define the incident eligible population**

| Parameter | Value | Source |
|---|---|---|
| Annual number of live births in England | 577,046 | Office for National Statistics (31) |
| Annual % change in number of live births | –1.8% | Office for National Statistics (31) |
| Incidence of CLN2 disease† | 0.00078% | Williams et al, 2017 (15) |

†As a proportion of live births.
Abbreviation: CLN2, neuronal ceroid lipofuscinosis type 2.

The eligible population in each of the first 5 years is presented in Table 93.

**Table 93: Eligible population**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Prevalent eligible population | 34 | – | – | – | – |
| Incident eligible population | 5 | 4 | 4 | 4 | 4 |

### B.3.15.2. Resources

Costs and assumptions used in the budget impact analysis are the same as those used in the cost-effectiveness model (Section B.3.5); the annual cost in each of the first five years for each of cerliponase alfa and standard of care (SoC) is based on the undiscounted outputs of the cost-effectiveness model for the first five years.

Estimates of budget impact include costs associated with drug acquisition and administration, background resource use, infection, adverse events, progressive symptoms and residential care.

### B.3.15.3. Uptake and market share

Clinical experts have confirmed that, of the 36 patients in the UK offered treatment with cerliponase alfa, one has declined treatment. The uptake of cerliponase alfa is therefore estimated to be 97.22%[k].

k Calculated as 35 divided by 36.


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**Table 94: Uptake and market share**

| Technology | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Eligible population | 39 | 4 | 4 | 4 | 4 |
| Cerliponase alfa | 97.2% | 97.2% | 97.2% | 97.2% | 97.2% |
| SoC | 2.8% | 2.8% | 2.8% | 2.8% | 2.8% |

### B.3.15.4. Estimated annual budget impact

The net budget impact associated with the introduction of cerliponase alfa in each of the first five years is presented in Table 95 and Table 96 for the analyses including and excluding discounts to the cerliponase alfa list price, respectively. When the considered discounts are included, the net budget impact does not exceed the budget impact threshold of £20 million per year in any of the first three years.

**Table 95: Expected budget impact – discounted price for cerliponase alfa**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Eligible population for treatment with cerliponase alfa | 38 | 4 | 4 | 4 | 4 |
| Population expected to receive cerliponase alfa | 36 | 4 | 4 | 4 | 4 |
| Cost of treatment pathway without cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost of treatment pathway with cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net budget impact | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 96: Expected budget impact – list price for cerliponase alfa**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Eligible population for treatment with cerliponase alfa | 38 | 4 | 4 | 4 | 4 |
| Population expected to receive cerliponase alfa | 36 | 4 | 4 | 4 | 4 |
| Cost of treatment pathway without cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost of treatment pathway with cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net budget impact | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |


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## Appendices

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection, and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Published cost effectiveness studies
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# Summary of Information for Patients (SIP):

# The pharmaceutical company perspective

## What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

# Section 1: Submission summary

## 1a) Name of the medicine

Both generic and brand name.

Brineura® (cerliponase alfa▼).

## 1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Cerliponase alfa is a medicine for treating neuronal ceroid lipofuscinosis type 2 (CLN2 disease), an inherited condition in children that leads to progressive brain damage.

## 1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

European Medicines Agency (EMA) approval was granted on 30th May, 2017 (1). The UK marketing authorisation was granted on 1st January, 2021 by the Medicines and Healthcare products Regulatory Agency (MHRA) for cerliponase alfa for the treatment of CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency (2).

## 1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Grants awarded to Batten Disease Family Association (BDFA) over the course of the past 3 years, assessed and approved independently by the BioMarin Commercial team, came to the total amount of £218,466.

**Table 1: Grants awarded to the Batten Disease Family Association (2020–2023)**

| Description/purpose of activity | Date | GBP |
|---|---|---|
| Support BDFA's project on collection, analysis and reporting the efforts of COVID-19 on families on cerliponase alfa | 08.05.20 | 31,926 |
| Support BDFA's project on Batten Disease awareness day campaign | 26.05.20 | 3,000 |
| Charitable donation to support travel costs and accommodations for families of patients receiving cerliponase alfa | 20.06.20 | 20,000 |
| Support project aiming at awareness of CLN2 Batten disease and the BDFA across Scotland, Wales, and Northern Ireland - Regional communications and awareness project | 30.09.20 | 30,000 |
| Support BDFA's new institutional website, which includes a scientific and medical research and educational section | 09.03.21 | 20,000 |
| Charitable donation to support travel costs and accommodations for families of patients receiving cerliponase alfa | 18.10.21 | 10,000 |
| Support the institution to set up a study looking into the background for late diagnosis in CLN2 and CLN3 in the UK and its impact on families - part 1 | 04.11.21 | 25,000 |
| Charitable donation to support travel costs and accommodations for families of patients receiving cerliponase alfa | 29.04.22 | 5,000 |
| Support the BDFA family conference | 26.6.22 | 15,000 |
| Charitable donation to support travel costs and accommodations for families of patients receiving cerliponase alfa | 28.07.22 | 5,000 |
| Regional patient advocacy work new Batten treatment centres | 12.09.22 | 2,940 |
| Support the BDFA to attend an international conference and make key contacts with other patient organizations | 30.09.22 | 2,500 |
| Support the institution to set up a study looking into the background for late diagnosis in CLN2&3 in the UK and its impact on families - part 2 | 30.09.22 | 10,000 |
| Charitable donation to support travel costs and accommodations for families of patients receiving cerliponase alfa | 16.02.23 | 10,000 |
| Support the institution to set up a study looking into the background for late diagnosis in CLN2 and CLN3 in the UK and its impact on families - part 3 | 16.02.23 | 10,000 |
| Support the institution's activities to support treatment centres across the UK - new treatment centres | 16.02.23 | 4,000 |
| Support the BDFA Family Conference 2023 - event was cancelled and funds were reallocated to support families with higher needs for psychological support | 16.02.23 | 15,000 |
| Refund related to support to BDFA attendance at international conference as staff was unable to attend | 09.23 | –2,940 |
| Reimbursement of expenses for meetings organised by BMRN with BDFA | H2 2023 | 295 |
| Fees for participation in Advisory Board events organised and sponsored by BMRN | H2 2023 | 1,745 |

Abbreviations: BDFA, Batten Disease Family Association; UK, United Kingdom.

# Section 2: Current landscape

## 2a) The condition – Clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

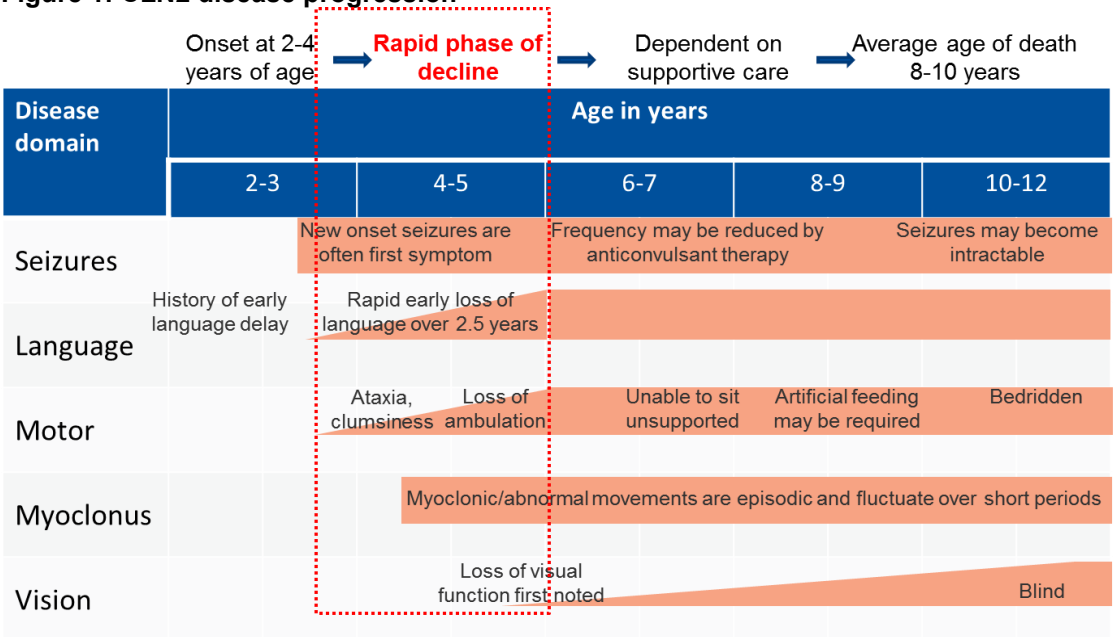
Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is an inherited condition in children that leads to progressive brain damage. It is caused by gene changes that affect important body enzymes, leading to brain cell damage. Symptoms usually start between two to four years of age and get worse quickly. Children lose their ability to talk and walk, have trouble moving, feel pain, lose memory, lose their sight, and experience early death.

After symptoms begin, the decline is rapid. Seizures, trouble talking, and losing abilities usually start around three years, leading to severe problems within about 2.5 years. Children might need wheelchairs and lots of care. They face challenges like infections, difficulties eating, sleep problems, and declining health (Figure 1). The majority of children with CLN2 disease become bedridden and blind, and die between the age of 8 years and early adolescence (3-7).

Around 10% of cases have an 'atypical' form. These patients' symptoms are slightly different, their disease usually beginning at an older age and becoming worse more slowly, and their first symptoms can at first be slightly different. These individuals might live longer (8, 9).

**Figure 1: CLN2 disease progression**




CLN2 disease is very rare and it affects around 50 people, mostly children, in England. Each year, around five to six babies are born with this condition in England.

This disease severely limits a person's ability to live a normal life, often starting in early childhood. It heavily impacts their quality of life and places a heavy burden on parents,

caregivers, siblings, and the whole family. Taking care of someone with CLN2 disease brings financial challenges, such as reduced income due to caregiving, expenses for home changes and special care, and costs for treatments and support.

## 2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosing CLN2 disease can take time. The early symptoms — like seizures, language delays, and motor skill issues — can be linked to various other conditions. This often leads to misdiagnosis because CLN2 disease is very rare. Doctors, and especially those outside specialist centres, might not know much about the disease and its early signs. This can cause a delay of several years before getting the right diagnosis (10-13).

To diagnose CLN2 disease, a doctor usually orders a blood test to check the TPP1 enzyme activity (9). This quick single test confirms the disease, and no other tests are needed to start treatment with cerliponase alfa.

## 2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The National Health Service (NHS) is offering cerliponase alfa for CLN2 disease through a managed access agreement. This provides patients access to the drug while further data collection is carried out that allows committees to make definitive decision at the end of the time-limited agreement.

Cerliponase alfa is the only approved treatment for CLN2 disease, and no alternative treatments currently exist. Before this medicine, there were no cures, and a diagnosis was always fatal. No treatments targeting the root cause were available before cerliponase alfa and CLN2 disease management was focused on symptom relief and supportive care.

## 2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about patient needs and disease experiences. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Caring for a child with CLN2 disease is an incredibly demanding journey. Families affected by this condition experience a wide range of challenges, both emotionally and practically. Patient-based evidence was sourced from patient advocates and patient families. Sources of patient-based evidence used in the reappraisal of cerliponase alfa include results from a questionnaire published by Schulz and colleagues, 2020 (15), and a BioMarin-funded patient advocate advisory board held in July 2023 (12), which included four advocates, three of whom were carers.

Evidence from patient advocates and families (12, 15) highlights the challenges of caring for a child with CLN2 disease. Caregivers face emotional, physical, and financial struggles, dealing with disrupted sleep, back pain, anxiety, and exhaustion (15). Accessing specialised support is difficult.

Families experience frustration, anger, and uncertainty during the diagnosis journey (12, 15). Primary caregivers dedicate about 96 hours a week to care, averaging around five hours of sleep per night (12, 15).

Family relationships can become strained, with some siblings struggling to understand the affected child's condition, causing fear and frustration (12, 15). Balancing parental attention between children also becomes challenging, leaving some siblings feeling excluded and anxious (12).

Financially, caregivers may need to leave work due to the demands of caring for their child (15). Added expenses and funding delays create further strain. Families often cover healthcare costs for specialised equipment and home adjustments (12, 15).

Children with CLN2 disease find it hard to attend mainstream schools due to changes in vision, language, and mobility (12). Finding suitable educational support presents challenges, especially during the early phase of uncertain diagnosis (12).

Social support varies, with some caregivers feeling isolated while others receive help from family, friends, and community groups (15). Families face tough choices when faced with a diagnosis of CLN2 disease, including potential terminations during pregnancy and genetic testing of siblings (15).

Caregiver burden increases as CLN2 disease progresses. Caregivers in later stages reported more caregiving hours and less sleep (15). Despite the challenges, caregiver life satisfaction, though lower than parents of healthy children, remains relatively stable, with parents accepting the situation and dealing with it for the sake of their children (15).

# Section 3: The treatment

## 3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

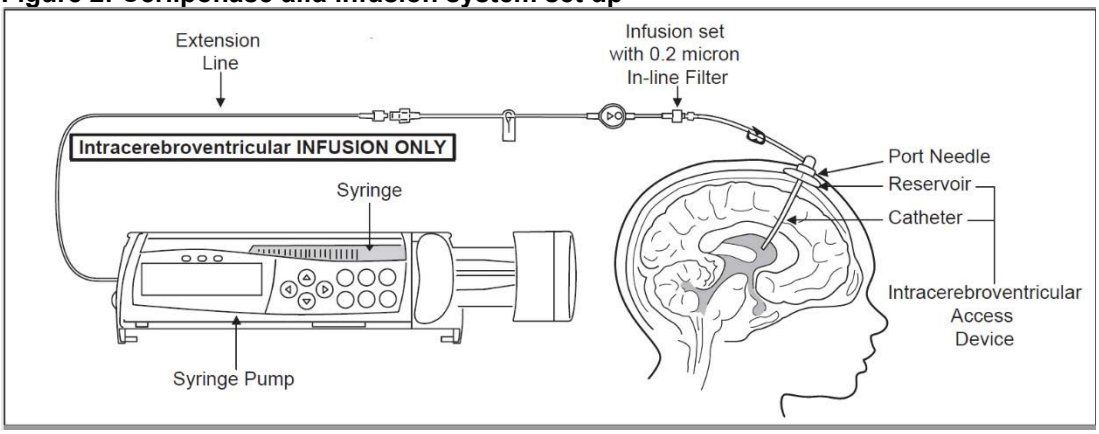
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Patients with CLN2 disease lack an essential brain development enzyme called tripeptidyl-peptidase-1 (TPP1). Cerliponase alfa acts as a substitute for TPP1, the missing enzyme (16). It is the only approved treatment directly addressing the root cause of CLN2 disease and has marked a significant shift in how the disease is managed.

The medicine is infused directly into the brain (intracerebroventricular infusion; Figure 2). This is done to bypass the blood-brain barrier, a protective barrier that separates the blood stream from the brain and prevents substances, such as medicines, from entering brain tissue. Cerliponase alfa is notable for being the first treatment directly infused into the brain using the intracerebroventricular route.

**Figure 2: Cerliponase alfa infusion system set up**




## 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☐Yes

☒No

**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**

Not applicable.

## 3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Cerliponase alfa is infused directly into the brain. Before the first infusion, the patient will need to have surgery to implant a delivery access device, which runs from the outside of the skull through to the fluid cavity in the brain where the medicine is delivered to.

The infusions are given once every two weeks by a healthcare professional knowledgeable about giving medicines into the brain in a specialised hospital setting (2). The recommended dose of cerliponase alfa for CLN2 is 300 mg for children two years or older (2). In patients younger than 2 years old, lower doses are recommended (Table 2). To reduce the risk of reaction during infusion, patients might receive other medicines before or during treatment with cerliponase alfa or the infusion may be slowed down (2). The treatment can continue for as long as the patient benefits from it.

**Table 2: Dose and volume of cerliponase alfa**

| Age groups | Total dose (volume) administered every other week |
|---|---|
| Birth to 6 months | 100 mg (3.3.ml) |
| 6 months to 1 year | 150 mg (5.0 ml) |
| 1 year to 2 years | 200 mg (6.7 ml) (first 4 doses)<br>300 mg (10.0 ml) (later doses) |
| 2 years and older | 300 mg (10.0 ml) |

In England there are six specialised centres where cerliponase alfa treatment can be administered, to which patients and their caregivers must travel. These are: Great Ormond Street Hospital (GOSH) in London; Birmingham Children's Hospital; Bristol Royal Hospital for Children; Manchester University Hospital; Royal Victoria Infirmary in Newcastle, and Salford Royal Hospital.

## 3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The main evidence for cerliponase alfa for CLN2 disease comes from three studies: 190-201, 190-202, and 190-901. The first study tested 24 children (aged 3 to 16 years) in four countries (Italy, Germany, England, and the US) who were treated with cerliponase

alfa for 48 weeks. These children then continued into an extension study, 190-202, for up to 240 weeks. The third study, 190-901, used historical records to look at how CLN2 disease progressed in people who didn't get any treatment (known as natural history). The results from 190-901 were compared with the data from 190-201/202 using statistical methods, to see how effective cerliponase alfa is compared with no treatment.

Subjects of less than three years of age were not included in Study 190-201/202, because not enough evidence was available for cerliponase alfa when this study started and therefore it was not ethical to include very young patients in the trial. Upon more cerliponase alfa evidence becoming available by the start of Study 190-203, this trial also included patients younger than three years, and provided additional long-term clinical evidence for celiponase alfa for CLN2 in a population more generalisable to the UK.

Additional information was collected from an extended analysis of study 190-202, safety studies, disease registries, and real-world evidence.

## 3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results have shown that cerliponase alfa slows down the rapid progression of CLN2 disease.

A clinical rating scale (CLN2 scale) was developed to assess motor (M), language (L), vision (V), and seizure (S) domains, with a total score ranging from 0 to 12. Higher scores indicate better health. Motor and language are the earliest domains to lose function and are a meaningful measure of CLN2 disease burden. The motor and language (ML) subscale, scored from 0 to 6, was therefore used to specifically gauge disease progression.

In an initial analysis of 190-202 cerliponase alfa was shown to provide a clinically relevant treatment effect in patients with CLN2 disease. Almost two-thirds of participants (65%) either had no change or an improvement in ML score after 48 weeks of treatment, in a condition where rapid progression is typical. A large proportion of participants (87%) responded to treatment, defined as not having a two-point decline on the ML scale after 48 weeks of treatment (14, 17).

New evidence has demonstrated that cerliponase alfa can cause long-term stability, significantly slowing disease progression in the ML scale. Extended analysis of 190-202 indicated that cerliponase alfa's benefit persisted over up to six years of follow-up. In this analysis, 47% of treated individuals did not experience a two-point decline in ML score, compared with 6% of untreated individuals (17). Cerliponase alfa treated participants were also 96% less likely to die than untreated participants (17).

The impact of starting treatment in patients at earlier stages of CLN2 disease was shown in Study 190-203. The seven patients who had no visible CLN2 symptoms at the time they started cerliponase alfa treatment, were five times less likely to experience worsening disease compared with untreated patients. After 145 weeks of treatment, 100% of the untreated individuals had CLN2 disease progression, compared with 43% of cerliponase alfa-treated participants (18). Furthermore, analysis of brain images showed that treated participants in Study 190-203 that started treatment before they turned 3 years old, did not have any brain decay. Together, this evidence suggests that starting cerliponase alfa earlier is associated with less disease progression and better survival outcomes.

Cerliponase alfa treated participants did not experience increased seizure severity (19). Doctors who have experience of treating patients with CLN2 confirmed that the number of patients hospitalised or needing to see a doctor due to seizures was also decreasing (19). Cerliponase alfa treated patients also did not experience increases in the frequency and severity of movement disorders (18, 19).

## 3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patient-reported outcomes have been captured using various questionnaires to understand how treatment with cerliponase alfa impacts affected children's development and their health-related quality of life. Interpreting the data was challenging due to the lack of published information for comparison, however all the responses suggested that the treatment did not hinder the children's development or lower their life quality.

Since the routine availability of cerliponase alfa treatment from 2019, patient and healthcare proffessional feedback and preferences have been gathered through three advisory boards (12, 13, 19). Patient advocates witnessed better outcomes when treatment began earlier for children with CLN2 disease (12). Comparing siblings diagnosed and treated at different times highlighted the clear benefits of early intervention (12). Those who received early treatment led healthier lives compared with those treated later, who needed more constant care (12).

The treatment showed multiple positive effects: improving language skills, boosting confidence, and maintaining good mental health, despite the disease's progression. Overall, cerliponase alfa significantly enhanced the quality of life for patients and their families.

Healthcare professionals specialising in CLN2 disease treatment also noted the positive impact of cerliponase alfa (13). They found that seizures were easier to manage in treated patients, with seizures occurring less frequently and being less severe (13). In the past, seizures often led to hospitalisation, but this was reduced in patients receiving cerliponase

alfa (13). This improvement in seizure management positively affected families, allowing them to engage in normal activities like outings and holidays, significantly enhancing their quality of life (12).

## 3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Overall, cerliponase alfa safety studies demonstrated that treatment was generally well tolerated and had an acceptable safety profile in children with CLN2 disease.

The most common side effects with cerliponase alfa treatment (which may affect more than one in five people) are pyrexia (fever), low levels of protein in cerebrospinal fluid (the fluid in the brain and spinal cord), electrocardiogram (ECG) abnormalities (a test of the heart's activity), vomiting, upper respiratory tract infections (nose and throat infections), and hypersensitivity (allergic) reactions.

## 3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Cerliponase alfa is the first and only medicine that has been approved for the treatment of CLN2 disease. It is the only treatment option (pharmacological or otherwise) that addresses the underlying biological cause of this severe, rapidly progressing, and devastating disease, restoring TPP1 activity in the brain and thus restoring cellular function.

Results from the clinical studies provide evidence on the effectiveness of cerliponase alfa treatment for CLN2 disease. These results demonstrate that cerliponase alfa can stabilise or slow the progression of CLN2 disease, as demonstrated via the long-term stabilisation in ML score, in patients that are representative of patients seen in UK clinical practice.

Furthermore, results across the evidence base, including three long-term safety studies demonstrate that cerliponase alfa has a favourable safety profile and is generally well tolerated.

## 3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?

- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration

- What is the impact of any disadvantages highlighted compared with current treatments

As with all treatments, there can be side effects of treatment with cerliponase alfa. The most common side effects that patients receiving cerliponase alfa may experience include pyrexia, hypersensitivity (allergic) reactions, and vomiting.

Because cerliponase alfa is administered via intracerebroventricular infusion, patients will firstly need to undergo surgery to have the delivery device implanted.

Cerliponase alfa treatment must be administered by a trained healthcare professional in a specialist centre. With only six centres across England, patients and their caregivers may need to travel a considerable distance to receive treatment every two weeks.

## 3j) Value and economic considerations

**Introduction for patients:**

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

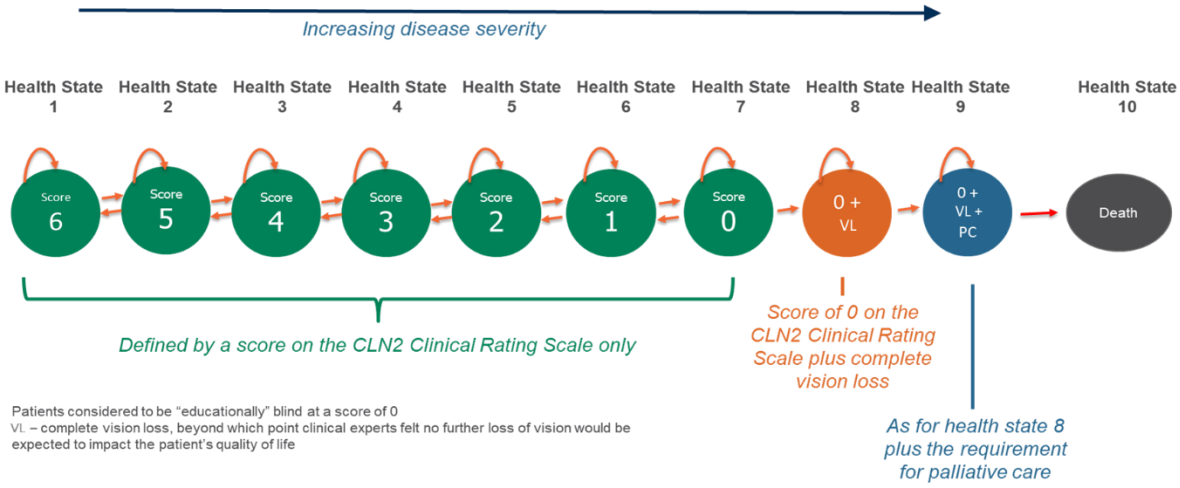
## How the health economic model reflects the condition

The health economic model captures the impact of CLN2 disease and its treatment with cerliponase alfa compared with standard of care. It does this by modelling how the two approaches affect the probabilities of disease progression and stabilisation. The health economic model is used to compare various outcomes, including the benefits of treatment that a person with CLN2 disease may experience, the impact of any side effects, and the cost to the NHS of treatment with cerliponase alfa versus standard of care. To simplify reality and allow an assessment to be made, the model uses health states which help to define some of these outcomes.

In this submission, ten mutually exclusive health states were included, through which people with CLN2 disease are expected to progress. These states were defined based on motor and language ability (measured using the CLN2 Clinical Rating Scale ML score), level of vision loss, and palliative care needs. This structure was designed to capture the chronic and progressive nature of CLN2 disease. A model schematic is presented in Figure 3.

The model looks at discrete time periods (called cycles). In each two-week cycle, patients will either move to a different health state or stay in the same health state. How patients move through health states depends on the treatment they receive and is based on each treatment's clinical data. The model also looks at the cost and quality of life impact of progressive symptoms and side effects (known as 'adverse events' [AEs]), and the quality of life impact on caregivers and siblings.

**Figure 3: Model schematic**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; PC, palliative care; VL, vision loss.

## Modelling how much a treatment improves quality of life

A 'utility' is the measure of the preference or value that an individual or society gives a particular health state. Utility studies enable the quantification of a disease's impact on patients' health-related quality of life. It is often difficult to obtain utility values for rare conditions, and conditions that cause progressive brain damage due to the cognitive burden required to collect the relevant information, and the limited size of patient/caregiver populations.

In this economic model, health state utility values were derived from a bespoke utility study in which descriptions of modelled health states were developed, validated by a clinical expert, and sent to eight clinical experts who completed the EQ-5D-5L

questionnaire (a standard questionnaire for assessing health-related quality of life) as a proxy for patients experiencing the health states (20).

Patients with higher motor and language scores are expected to have a better quality of life. As treatment with cerliponase alfa slows down CLN2 disease progression, patients will remain in health states associated with higher motor and language scores.

**Modelling how costs differ with cerliponase alfa vs standard of care treatment**

Standard of care treatment of CLN2 does not incur additional treatment costs. Patients treated with cerliponase alfa incur an additional cost to the NHS. In addition, the intracerebroventricular administration of cerliponase alfa is associated with costs for infusion, device insertion, and potential device replacements.

The economic model also considers the costs of side effects, visits to healthcare professionals, and the management of symptoms of CLN2.

**Uncertainty**

All economic modelling is associated with uncertainty. As CLN2 is an ultra-rare condition, data is limited. For this health economic model, data has been derived from the best available sources – however, assumptions have been made.

To assess the impact of any uncertainties and assumptions, values for these data inputs were varied and the model calculations re-run.

**Cost-effectiveness results**

The cost-effectiveness results are based on calculations using a cerliponase alfa price with a confidential discount which has been offered to the NHS.

In line with the summary of product characteristics, the drug dose and number of vials of cerliponase alfa required is modelled to be age dependent.

Based on the results of the cost-effectiveness model it is expected that in people with CLN2 disease, cerliponase alfa is a cost-effective treatment option, when compared with standard of care.

**Additional factors**

People with CLN2 are expected to experience a significant impact on the length and quality of life compared with the general population. The economic model captures the expected duration and quality of life for an average person with CLN2 receiving treatment with cerliponase alfa or standard of care.

Nevertheless, it is not possible to capture the full impact of treatment with cerliponase alfa. Due to the complex and rare nature of CLN2 disease, there are many additional benefits of cerliponase alfa treatment that cannot be captured by the economic model. These are discussed further in Section 3k.

## 3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

**Innovation**

The direct administration of cerliponase alfa enzyme replacement therapy to the brain is essential for CLN2 disease, so that the medicine can bypass the blood-brain barrier (the protective barrier that separates the blood stream from the brain and prevents substances from entering brain tissue).

Cerliponase alfa's key innovation is its intracerebroventricular delivery route, making it the first enzyme replacement therapy infused directly into the brain. This groundbreaking technology, available since 2019, has significantly improved CLN2 disease management.

Before the availability of cerliponase alfa under the MAA, effective treatment options for patients with CLN2 were lacking, highlighting a significant unmet need given the condition's devastating impact on quality of life, and short life expectancy.

**QALY benefits not captured in the QALY calculation**

The value of cerliponase alfa to patients, families, society, and healthcare systems is characterised by its ability to stabilise or slow the progression of CLN2 disease. The full effect of benefits therefore go far beyond the direct health benefits on patients with CLN2 disease and may not be captured in the calculation of the quality-adjusted life year (QALY).

Treatment with cerliponase alfa substantially reduces the progression of CLN2, minimising the need for constant revisions of care. Therefore, cerliponase alfa is likely to have significant benefits to patients other than health, including education, mental health, and societal contributions.

Additional benefits should be considered for carers and the families of patients who will be able to benefit society by improved employment and family life. Caregivers are generally the parents of children with CLN2. Caring for a child with CLN2 can have a large impact on caregiver mental health; parent representatives have described feelings of isolation, time anxiety, and anxiety for the future. CLN2 also has a large impact on siblings of affected children with siblings experiencing psychological effects and major anxieties. Treatment with cerliponase alfa can alleviate such pressures and anxieties by stabilising disease progression, and stabilising symptoms. Ultimately, treatment will have a significant effect on the quality of life experienced by patients with CLN2, their caregivers, and their families.

## 3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

| |
|---|
| No issues relating to equity or equality that are relevant to this evaluation have been identified. |

# SECTION 4: Further information, glossary and references

## 4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on cerliponase alfa from the MHRA:

- Summary of product characteristics – https://mhraproducts4853.blob.core.windows.net/docs/a6020e19f71a15e9056ac0e1fb08bfd56bd6c882
- Patient information leaflet – https://mhraproducts4853.blob.core.windows.net/docs/8ecbb0f30fffeaf5b2d51d4c91194e7b2d2f9204

Further information on the original appraisal HST12 (2017):

- https://www.nice.org.uk/guidance/hst12
- Managed access agreement – https://www.nice.org.uk/guidance/hst12/resources/managed-access-agreement-pdf-6968825245

Further information on CLN2 and patients/family support available via the Batten Disease Family Association:

- http://www.bdfa-uk.org.uk/
- http://www.bdfa-uk.org.uk/cln2-disease-late-infantile/
- http://www.bdfa-uk.org.uk/wp-content/uploads/2022/01/BDFA-A4-CLN2-Leaflet-2022.pdf

Further information on NICE and the role of patients**:**

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

## 4b) Glossary of terms

**Adverse event:** An unfavourable and unintended observation that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe

**Ataxia:** Loss of muscle control that causes clumsy movements

**Blood brain barrier:** A tight layer of cells that defend the brain from harmful agents that could cause damage

**Cerliponase alfa:** An enzyme replacement therapy for CLN2 that is administered via a specialised infusion, every 14 days

**CLN2:** An ultra-rare and rapidly progressing neurodegenerative disorder in children

**CLN2 Clinical Rating Scale:** Consists of four domains (motor, language, vision, and seizures) and enables the quantification of clinical progression of CLN2 with each function evaluated on a scale of 0–3, giving a total combined score between 0–12. As loss of motor and language (ML) function are the primary symptoms of CLN2 progression, a subscale of the CLN2 rating scale, **the ML scale**, is often employed to assess patient's disease progression

**Confidence interval (CI):** A range of values that you can be 95% certain contains the true mean of the population

**Clinical trial/clinical study**: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease

**Cerebrospinal fluid (CSF):** A clear, colourless body fluid found within the tissue that surrounds the brain and spinal cord

**Enzyme:** Proteins that help speed up chemical reactions in the human body

**Enzyme replacement therapy (ERT):** A medical treatment whereby replacement enzymes are given to patients who suffer from chronic conditions resulting from enzyme deficiencies or malfunction

**EQ-5D-5L:** A questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

**Hypersensitivity:** An excessive or abnormal sensitivity to a substance. If a person is hypersensitive to a certain drug, they will often suffer a severe allergic reaction if given the drug

**Intracerebroventricular (ICV) infusion:** A route of administration for drugs via injection directly into the brain. This route of administration is often used to bypass the blood-brain barrier

**Managed access agreement (MAA):** A time limited agreement set out by NICE that establishes the conditions under which people will be able to have NHS funded treatment, and how data will be collected to address the uncertainties in the clinical/cost-effectiveness data

**Myoclonus:** A sudden, brief, and involuntary twitching or jerking of a muscle or group of muscles

**National Institute for Health and Care Excellence (NICE):** An independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England

**Pyrexia:** This event, also known as fever, is an increase in the body temperature of an individual beyond the normal range

**Quality-adjusted life year (QALY):** A measure of disease burden that includes the length and quality of life

**Quality of life**: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living

**Standard of care**: Treatment that is accepted and widely used by medical experts and healthcare professionals for a certain type of disease

## 4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:


1. European Medicines Agency (EMA). Brineura - European Public Assessment Report. 2017.

2. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of product characteristics. Cerliponase alfa. Available at: https://mhraproducts4853.blob.core.windows.net/docs/112db1af1e84a09fcfd26d0133b7f4b2741770ed (last accessed September 2023). 2023.

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12. BioMarin. Data on File: Cerliponase alfa for the treatment of CLN2. Virtual advisory board with patient advocates from England. 24th July 2023. . 2023.

13. BioMarin. Data on File: Cerliponase alfa for the treatment of CLN2 - cost-effectiveness modelling. Virtual advisory board with healthcare proffesionals from England. 3rd July 2023. 2023.

14. National Institute for Health and Care Excellence (NICE). Final evaluation document. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. 2019.

15. Schulz A, Jain M, Butt T, Ballinger R, Eliasson L, Macey J, et al. The challenges of living with and caring for a child or children affected by neuronal ceroid lipofuscinosis type 2 disease: In-depth family surveys in the United Kingdom and Germany. Journal of Inborn Errors of Metabolism and Screening. 2020;8.

16. European Medicines Agency. Brineura - Summary of Product Characteristics. 2022.

17. Schulz A, Specchio N, de Los Reyes E, Gissen P, Nickel M, Trivisano M, et al. Safety and efficacy of cerliponase alfa in children with neuronal ceroid lipofuscinosis type 2 (CLN2 disease): an open-label extension study. Lancet Neurol. 2024;23(1):60-70.

18. Schulz A, Specchio N, De Los Reyes E, Gissen P, Slasor P, Bondade S, et al. Cerliponase alfa for the treatment of CLN2 disease in a patient cohort including children <3 years old (presented at 18th International Congress on Neuronal Ceroid Lipofuscinoses, Hamburg, 2023). 2023.

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Highly Specialised Technology

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

# Clarification questions

**February 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6145 cerliponase alfa clarification questions 150224 [Redacted] | V1.0 | No – [Redacted] | 15/02/2024 |

# Section A: Clarification on effectiveness data

### A1. Priority question: On Page 43 of the CS (in the clinical effectiveness summary) it is stated that: "Long-term CLN2 disease stabilisation was achieved via cerliponase alfa treatment, as demonstrated via clinically meaningful and statistically significant slowing of disease progression". Please clarify the meaning of this sentence given that disease stabilisation is not the same as slowing of disease progression.

One of the key clinical uncertainties considered by the committee during their evaluation of HST12 was cerliponase alfa's capacity to provide long-term disease stabilisation. Whilst the evidence for complete stabilisation of disease was not captured in the clinical effectiveness evidence, cerliponase alfa treatment has been shown to provide long-term stabilisation of key symptoms of the CLN2 disease process.

Since HST12, the extended follow-up and additional evidence for cerliponase alfa in CLN2 disease presented in the submission, provides significant and meaningful evidence for cerliponase alfa's effect on the CLN2 disease process. Cerliponase alfa was also shown to delay the CLN2 disease process, with slowing of progression shown via ML scale assessments in treated patients irrespective of their starting ML score. Furthermore, there is significant evidence for long-term stabilisation of the CLN2 disease process in patients diagnosed at earliest symptoms, as demonstrated for participants in Study 190-203 who initiated treatment with an ML score of 6 and experienced no changes in ML score over the maximum 145 weeks of study follow-up (1). Specifically, long-term stabilisation of neurological deterioration was shown in participants treated at an early age, who did not present any symptomatic progression, deterioration, or show clinically significant loss of grey matter volume over the long-term follow-up.

Seizures are one of the most common early symptoms of CLN2 disease, frequently becoming more severe, more frequent, and resistant to anti-epileptic drugs (AED) as the disease evolves (2, 3). Furthermore, several commonly used AEDs (such as carbamazepine and phenytoin) may be associated with deterioration of motor functions in patients with CLN2 disease (4, 5). Cerliponase alfa treated participants in the presented clinical effectiveness studies did not show significant deterioration or progression of seizure symptoms when compared with natural history patients (see A15 for additional evidence). This symptomatic seizure stabilisation in treated patients was supported during advisory boards with clinicians and patient advocates, who emphasised that the stabilising treatment

effect on seizures has had a crucial impact on maintaining the quality of life for patients, their families, and carers (6, 7).

Patients with CLN2 disease have progressive loss of vision and are typically blind by the age of 7–10 years (2). ICV administration of cerliponase alfa is not expected to have an effect on the retina and decline in vision accompanied by progressive retinal degradation has been documented in patients receiving treatment (see A14 for additional evidence) (8). Therefore, although long-term stabilisation of some symptoms and the disease process has been shown, lifelong CLN2 disease stabilisation may not be claimed, with inevitable visual deterioration irrespective of ML starting score.

The value of cerliponase alfa to patients with CLN2, families, society, and healthcare systems is characterised by its ability to stabilise or slow the progression of CLN2 disease key symptoms, which has not been possible with other approaches.

## *Clinical data requests*

### A2. Priority question: For studies 190-201, -202, and -203 please provide the "Tabulations of Individual Response Data" referred to in the CSRs (such as Section 11.4.4 of the 190-202 CSR. Please note: the links in the documents do not work). Please also provide these data for the MAA cohort.

The following 'Tabulations of Individual Response Data' referred to in the 190-201 CSR are included in the reference pack:

- CLN2 Disease Rating Scales: Listing 16.2.6.1
- CLN2 Disease Based Quality of Life: Listing 16.2.6.2
- PedsQL – Parent Report for Toddlers: Listing 16.2.6.3
- PedsQL – Parent Family Impact: Listing 16.2.6.4,
- Denver II Development: Listing 16.2.6.5
- MRI Results: Listing 16.2.6.6
- Videotaping: Listing 16.2.6.7.

The following 'Tabulations of Individual Response Data' referred to in the 190-202 CSR are included in the reference pack:

- CLN2 Disease Rating Scales: Listing 16.2.6.1

- CLN2 Disease Based Quality of Life: Listing 16.2.6.2
- PedsQL – Parent Report for Toddlers: Listing 16.2.6.3
- PedsQL – Parent Family Impact Listing: 16.2.6.4
- Denver II Development: Listing 16.2.6.5
- MRI Results: Listing 16.2.6.6
- Retinal Anatomy using OCT: Listing 16.2.6.7
- Visual Acuity: Preferential Looking Testing: Listing 16.2.6.8
- EQ-5D-5L Health Questionnaire: Listing 16.2.6.9
- Electroencephalogram: Listing 16.2.6.10

The following 'Tabulations of Individual Response Data' referred to in the 190-203 CSR are included in the reference pack:

- CLN2 Disease Rating Scales, ITT Population: Listing 16.2.6.1.1,
- CLN2 Disease Rating Scales, Matched Participants from 901: Listing 16.2.6.1.2
- MRI Results, ITT Population- Listing 16.2.6.2.1
- Visual Acuity: Preferential Looking Test, ITT Population: Listing 16.2.6.8.1

The 'Tabulations of Individual Response Data' are included in the [BioMarin-DataOnFile-Cerliponase alfa MAA _Database _SourceCut _Nov1.xlsx] file.

**A3. Priority question: The EAG would appreciate analyses pooling all data across the three main trials of cerliponase alpha (190-201/202, 190-203 and the MAA, as per the 'all patients' dataset used to inform transition probabilities in a scenario analyses in Section B.3.3.2 of the CS) so that a complete picture of its efficacy can be obtained. If feasible, please supply the following, using all data pooled across all three trials:**

1. **A tabulation of numbers and percentages of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline at each year of follow-up (similar to Appendix O Figure 1)**

2. **Kaplan-Meier curves for time to unreversed 2-point decline in ML score or score of zero (as in CS Figure 4)**

3. **Kaplan-Meier curves for time to ML score of zero (as in CS Figure 6)**

4. **An analysis of rate of decline in ML score (as in CS Table 27 and Figure 7A)**

**Please note that we do not expect these analyses to include comparisons with matched natural history patients, but would appreciate this being included, if it is feasible.**

Note that whilst studies 190-202 and 190-203 are prospective clinical trials, the MAA is a data collection agreement and not considered a clinical trial. The cerliponase alfa 'all patients' and matched natural history dataset therefore combines multiple data sources with inconsistent timepoints. Therefore, decline at each year of follow-up is defined by the time windows outlined in Table 1. Where multiple assessments occur in a time window, the assessment closest to the corresponding year was taken. The decline up to Year 6 is presented, as the longest follow-up in the matched natural history patients was six years. The number and percentage of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline at each year of follow-up is presented in Figure 1 and Figure 2 for the cerliponase alfa 'all patients' dataset and the matched natural history dataset, respectively.

**Table 1: Time definitions for analyses**

| Time point | Time-window for timepoint |
|---|---|
| Year 1 evaluation | Day 1 – Day 547 |
| Year 2 evaluation | Day 547 – Day 913 |
| Year 3 evaluation | Day 914 – Day 1278 |
| Year 4 evaluation | Day 1279 – Day 1643 |
| Year 5 evaluation | Day 1644 – Day 2008 |
| Year 6 evaluation | Day 2009 – Day 2374 |

**Figure 1: Change in CLN2-ML clinical rating scale score – (1:1 matched 'all patients')**

Year 1

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | 1 | | 1 | 1 | | 3 (8%) |
| 0 | 7 | 1 | 3 | 5 | 3 | 1 | 20 (54%) |
| -1 | 1 | | 3 | 2 | 1 | | 7 (19%) |
| -2 | | 2 | 4 | 1 | | | 7 (19%) |
| -3 | | | | | | | |
| -4 | | | | | | | |
| -5 | | | | | | | |
| -6 | | | | | | | |
| Total | 8 (22%) | 4 (11%) | 10 (27%) | 9 (24%) | 5 (14%) | 1 (3%) | 37 (100%) |

Year 2

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | 1 | | 1 | | 1 | 3 (9%) |
| 0 | 7 | 1 | 3 | 5 | 3 | | 19 (54%) |
| -1 | | | 3 | 3 | 1 | | 7 (20%) |
| -2 | | 1 | 4 | | | | 5 (14%) |
| -3 | | | 1 | | | | 1 (3%) |
| -4 | | | | | | | |
| -5 | | | | | | | |
| -6 | | | | | | | |
| Total | 7 (20%) | 3 (9%) | 11 (31%) | 9 (26%) | 4 (11%) | 1 (3%) | 35 (100%) |

Year 3

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | 1 | 1 | 1 | 3 (9%) |
| 0 | 6 | | 2 | 4 | 2 | | 14 (40%) |
| -1 | | 2 | 1 | 3 | 2 | | 8 (23%) |
| -2 | | | 7 | 2 | | | 9 (26%) |
| -3 | | | | | | | |
| -4 | | | 1 | | | | 1 (3%) |
| -5 | | | | | | | |
| -6 | | | | | | | |
| Total | 6 (17%) | 2 (6%) | 11 (31%) | 10 (29%) | 5 (14%) | 1 (3%) | 35 (100%) |

Year 4

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | 1 | | | 1 (5%) |
| 0 | 1 | | 2 | 2 | 2 | | 7 (37%) |
| -1 | | | | 3 | 2 | | 5 (26%) |
| -2 | | | 4 | 2 | | | 6 (32%) |
| -3 | | | | | | | |
| -4 | | | | | | | |
| -5 | | | | | | | |
| -6 | | | | | | | |
| Total | 1 (5%) | | 6 (32%) | 8 (42%) | 4 (21%) | | 19 (100%) |

Year 5

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | 1 | | | 1 (6%) |
| 0 | | | 1 | | 1 | | 2 (12%) |
| -1 | 1 | | | 3 | 2 | | 6 (35%) |
| -2 | | | 4 | 2 | | | 6 (35%) |
| -3 | | | | 2 | | | 2 (12%) |
| -4 | | | | | | | |
| -5 | | | | | | | |
| -6 | | | | | | | |
| Total | 1 (6%) | | 5 (29%) | 8 (47%) | 3 (18%) | | 17 (100%) |

Year 6

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | | | | |
| 0 | | | | | | | |
| -1 | | | 2 | 2 | 2 | | 6 (38%) |
| -2 | | | 1 | 3 | 1 | | 5 (31%) |
| -3 | 1 | | 2 | 2 | | | 5 (31%) |
| -4 | | | | | | | |
| -5 | | | | | | | |
| -6 | | | | | | | |
| Total | 1 (6%) | | 5 (31%) | 7 (44%) | 3 (19%) | | 16 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language.

**Figure 2: Change in CLN2-ML clinical rating scale score – (1:1 matched NH)**

Year 1

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | | | | |
| 0 | 2 | | 2 | | 1 | 1 | 6 (15%) |
| -1 | 2 | 1 | 1 | 2 | 2 | | 8 (21%) |
| -2 | 4 | 1 | 1 | 3 | 3 | | 12 (31%) |
| -3 | | 1 | 1 | 5 | | | 7 (18%) |
| -4 | | 1 | 5 | | | | 6 (15%) |
| -5 | | | | | | | |
| -6 | | | | | | | |
| Total | 8 (21%) | 4 (10%) | 10 (26%) | 10 (26%) | 6 (15%) | 1 (3%) | 39 (100%) |

Year 2

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | | | | |
| 0 | | | 1 | | | | 1 (4%) |
| -1 | 1 | 1 | | | 1 | 1 | 4 (16%) |
| -2 | 1 | | | | 2 | | 3 (12%) |
| -3 | 1 | | 1 | 5 | | | 7 (28%) |
| -4 | 1 | | 6 | | | | 7 (28%) |
| -5 | 1 | 1 | | | | | 2 (8%) |
| -6 | 1 | | | | | | 1 (4%) |
| Total | 6 (24%) | 2 (8%) | 8 (32%) | 5 (20%) | 3 (12%) | 1 (4%) | 25 (100%) |

Year 3

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | | | | |
| 0 | | | | | | | |
| -1 | | | | | | 1 | 1 (5%) |
| -2 | | | 1 | | 5 | | 6 (30%) |
| -3 | | | | 4 | | | 4 (20%) |
| -4 | | | 3 | | | | 3 (15%) |
| -5 | 1 | 1 | | | | | 2 (10%) |
| -6 | 4 | | | | | | 4 (20%) |
| Total | 5 (25%) | 1 (5%) | 4 (20%) | 4 (20%) | 5 (25%) | 1 (5%) | 20 (100%) |

Year 4

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | | | | |
| 0 | | | | | | | |
| -1 | | | | | | | |
| -2 | | | | | 2 | | 2 (40%) |
| -3 | | | | 1 | | | 1 (20%) |
| -4 | | | 1 | | | | 1 (20%) |
| -5 | | | | | | | |
| -6 | 1 | | | | | | 1 (20%) |
| Total | 1 (20%) | | 1 (20%) | 1 (20%) | 2 (40%) | | 5 (100%) |

Year 5

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | | | | |
| 0 | | | | | | | |
| -1 | | | | | | | |
| -2 | | | | | | | |
| -3 | | | | 2 | | | 2 (50%) |
| -4 | | | 1 | | | | 1 (25%) |
| -5 | | | | | | | |
| -6 | 1 | | | | | | 1 (25%) |
| Total | 1 (25%) | | 1 (25%) | 2 (50%) | | | 4 (100%) |

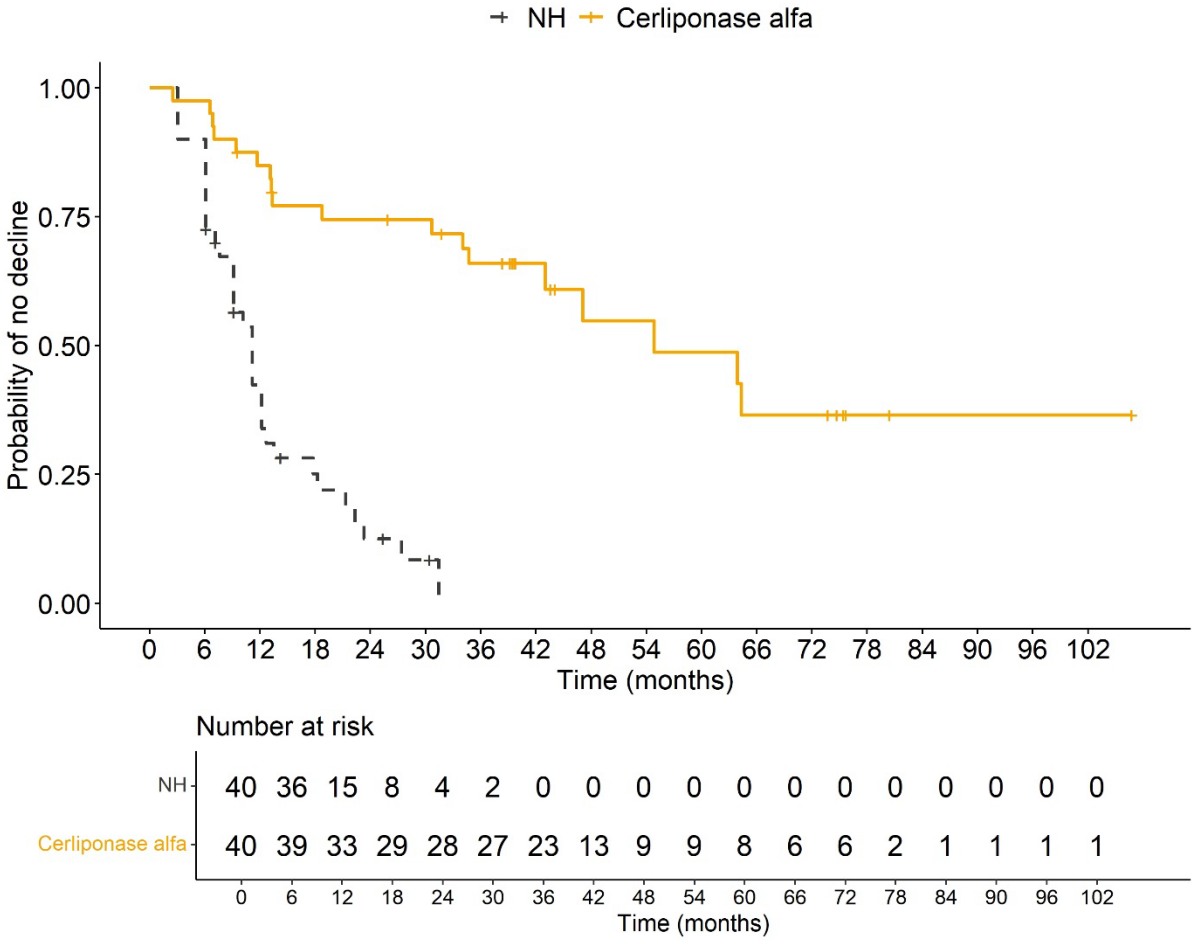
Year 6

| Change in CLN2-ML clinical rating scale score | Baseline CLN2-ML clinical rating scale score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | Total |
| 1 | | | | | | | |
| 0 | | | | | | | |
| -1 | | | | | | | |
| -2 | | | | | 2 | | 2 (50%) |
| -3 | | | | 1 | | | 1 (25%) |
| -4 | | | | | | | |
| -5 | | | | | | | |
| -6 | 1 | | | | | | 1 (25%) |
| Total | 1 (25%) | | | 1 (25%) | 2 (50%) | | 4 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; NH, natural history.

The Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-ML score or score of zero and summary are shown in **Figure 3** and Table 2, respectively.

**Figure 3: Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-ML score or score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; NH, natural history.

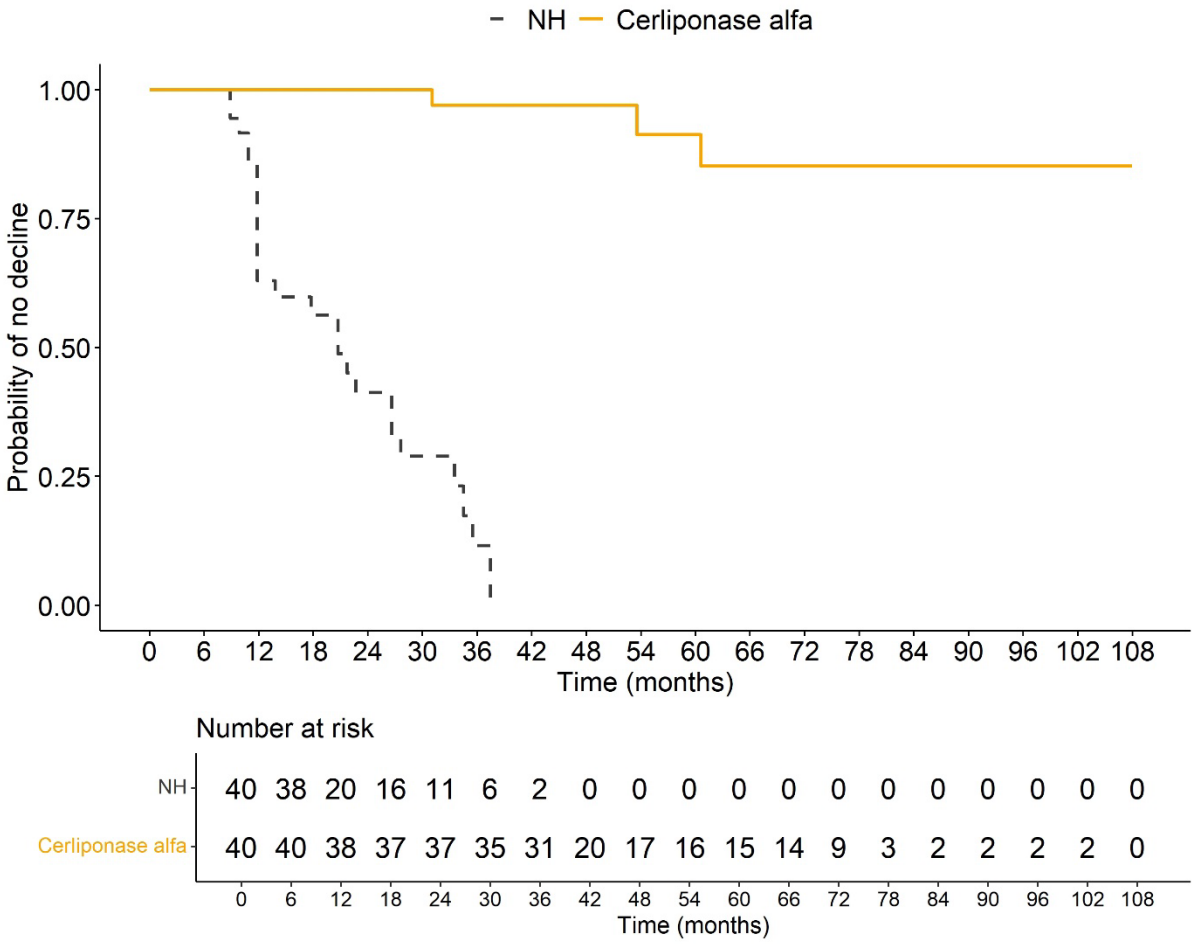
**Table 2: Kaplan-Meier curve summary for time to unreversed 2-point decline in CLN2-ML score or score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 18 | 54.9 (34.7, NR) | 0.139 (0.068, 0.287) | <0.0001 |
| NH | 40 | 34 | 11.2 (9.2, 12.2) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; NH, natural history; NR, not reached.

The Kaplan-Meier curve for time to CLN2-ML score of zero and summary are shown in Figure 4 and Table 3, respectively.

**Figure 4: Kaplan-Meier curve for time to CLN2-ML score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; NH, natural history.

**Table 3: Kaplan-Meier curve summary for time to CLN2-ML score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 3 | NR (NR, NR) | 0.005 (0.001, 0.040) | <0.0001 |
| NH | 40 | 27 | 20.7 (11.9, 27.6) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; NH, natural history; NR, not reached.

Table 4 presents the analysis of rate of decline in CLN2-ML score of the matched natural history patients and cerliponase 'all patients' at 48 weeks.

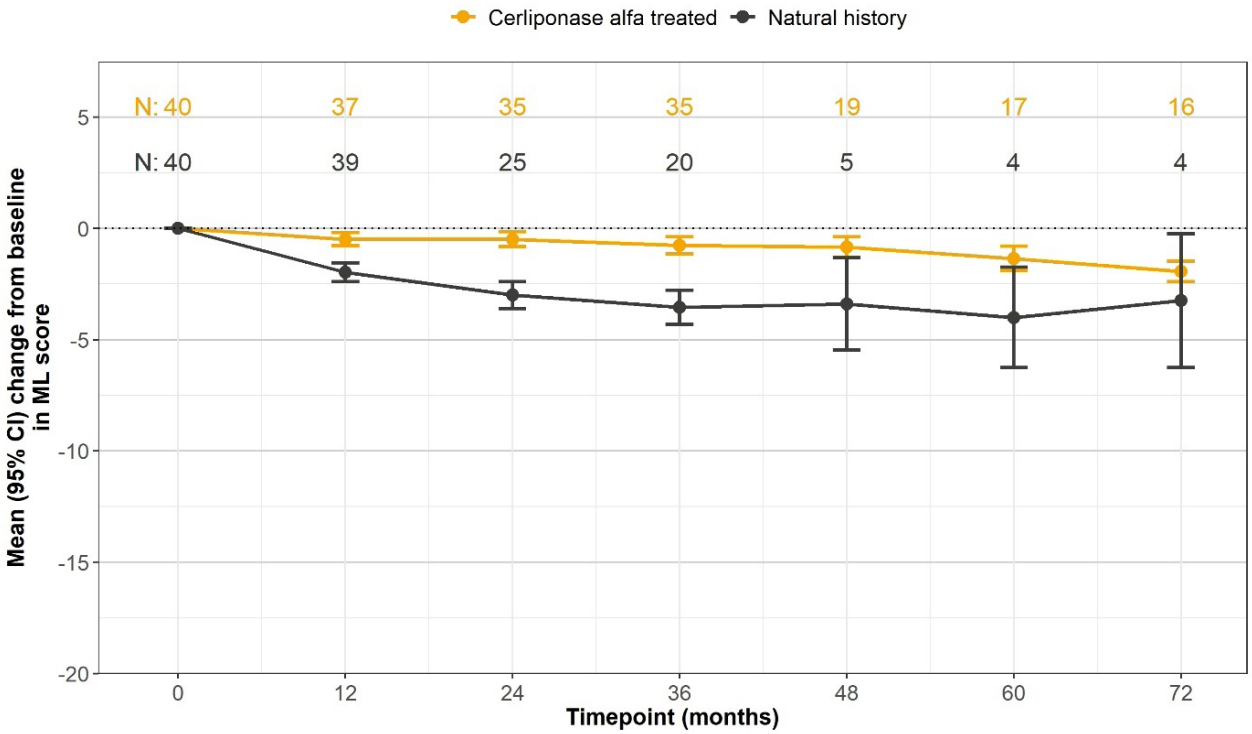
**Table 4: CLN2-ML scale – Rate of decline (1:1 matched NH and 'all patients')**

| Rate of Decline (Points/48 weeks) | NH | 'All patients' | Difference (NH–'all patients') | Two-sided p-value |
|---|---|---|---|---|
| ML total score | | | | |
| n | 40 | 40 | | |
| Mean (SD) | 1.26 (0.84) | 0.32 (0.61) | 0.95 | <0.0001 |
| (SE) | | | 0.16 | |
| Median | 1.14 | 0.29 | | |
| 25th, 75th Percentile | 0.58, 1.77 | 0, 0.45 | | |
| Min, Max | 0, 3.71 | –1.19, 3.25 | | |
| 95% CI | 1.00, 1.53 | 0.12, 0.51 | 0.62, 1.27 | |

Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; NH, natural history.

Using the same time windows as in Table 1, the change from baseline in CLN2-ML score at each year of follow-up is shown in Figure 5.

**Figure 5: Change from baseline in CLN2-ML score by year of follow-up (1:1 matched NH and 'all patients')**




Abbreviations: Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor language; NH, natural history.

**A4. Priority question: Please provide a summary of changes in full CLN2 rating scale scores (that is for full MLVS score) for trials 190-202, 190-203 and MAA, and, if possible, for the matched natural history cohort.**

1. **If possible, please supply the same tabulations and figures as listed in Question A3 for the full MLVS score.**

2. **If possible, please provide similar tabulations and/or Kaplan-Meier curves for each of the four components (motor, language, vision, seizures) separately.**

**CLN2-MLVS clinical rating scale score**

Using the same time windows as in Table 1, the number and percentage of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline at each year of follow-up is presented in Figure 6 and Figure 7 for the cerliponase alfa 'all patients' dataset, and in Figure 8 and Figure 9 for the matched natural history dataset.

**Figure 6: Change in CLN2-MLVS clinical rating scale score (1:1 matched 'all patients'); Year 1 to 3**

Year 1

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | 1 | | 1 | | | | | | | 2 (5%) |
| 2 | | | | | | | 1 | | | 1 | | | 2 (5%) |
| 1 | | 1 | | 1 | | 3 | 1 | | | | | | 6 (16%) |
| 0 | 5 | 2 | 2 | 2 | 3 | 1 | | | | | | | 15 (41%) |
| -1 | | | 2 | 2 | 2 | | | | 1 | | | | 7 (19%) |
| -2 | | | 1 | 1 | 1 | | | | | | | | 3 (8%) |
| -3 | | 1 | | 1 | | | | | | | | | 2 (5%) |
| -4 | | | | | | | | | | | | | |
| -5 | | | | | | | | | | | | | |
| -6 | | | | | | | | | | | | | |
| -7 | | | | | | | | | | | | | |
| -8 | | | | | | | | | | | | | |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | | | | | | | | | | | | | |
| Total | 5 (14%) | 4 (11%) | 5 (14%) | 8 (22%) | 6 (16%) | 5 (14%) | 2 (5%) | | 1 (3%) | 1 (3%) | | | 37 (100%) |

Year 2

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | 2 | 1 | | | 1 | | | 4 (11%) |
| 2 | | | | | | | 1 | | | | | | 1 (3%) |
| 1 | | 3 | | 2 | 1 | 1 | | | | | | | 7 (20%) |
| 0 | 4 | | 1 | 1 | 1 | | | | 1 | | | | 8 (23%) |
| -1 | 1 | | 2 | | 3 | 1 | | | | | | | 7 (20%) |
| -2 | | | 2 | 3 | 1 | | | | | | | | 6 (17%) |
| -3 | | | 1 | | | | | | | | | | 1 (3%) |
| -4 | | | | 1 | | | | | | | | | 1 (3%) |
| -5 | | | | | | | | | | | | | |
| -6 | | | | | | | | | | | | | |
| -7 | | | | | | | | | | | | | |
| -8 | | | | | | | | | | | | | |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | | | | | | | | | | | | | |
| Total | 5 (14%) | 3 (9%) | 6 (17%) | 7 (20%) | 6 (17%) | 4 (11%) | 2 (6%) | | 1 (3%) | 1 (3%) | | | 35 (100%) |

Year 3

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | 1 | 2 | | | 1 | | | 4 (11%) |
| 2 | | | | | 1 | 1 | | | | | | | 2 (6%) |
| 1 | | 1 | | | 1 | | | | | | | | 2 (6%) |
| 0 | 5 | | | 2 | | 1 | | | | | | | 8 (23%) |
| -1 | | | | 1 | 3 | 1 | | | 1 | | | | 6 (17%) |
| -2 | | 1 | 2 | 1 | 2 | | | | | | | | 6 (17%) |
| -3 | | | 3 | 1 | | | | | | | | | 4 (11%) |
| -4 | | | | 2 | | | | | | | | | 2 (6%) |
| -5 | | | | 1 | | | | | | | | | 1 (3%) |
| -6 | | | | | | | | | | | | | |
| -7 | | | | | | | | | | | | | |
| -8 | | | | | | | | | | | | | |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | | | | | | | | | | | | | |
| Total | 5 (14%) | 2 (6%) | 5 (14%) | 8 (23%) | 7 (20%) | 4 (11%) | 2 (6%) | | 1 (3%) | 1 (3%) | | | 35 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure.

**Figure 7: Change in CLN2-MLVS clinical rating scale score (1:1 matched 'all patients'); Year 4 to 6**

Year 4

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | 1 | | | | | | | 1 (5%) |
| 2 | | | | | | 1 | 1 | | | | | | 2 (11%) |
| 1 | | 1 | | | | | 1 | | | | | | 2 (11%) |
| 0 | | | | 1 | 2 | 1 | | | 1 | | | | 5 (25%) |
| -1 | | | | 2 | 1 | | | | | | | | 3 (16%) |
| -2 | | | | 1 | | 1 | | | | | | | 2 (11%) |
| -3 | | | 1 | | 1 | | | | | | | | 2 (11%) |
| -4 | | | 1 | | 1 | | | | | | | | 2 (11%) |
| -5 | | | | | | | | | | | | | |
| -6 | | | | | | | | | | | | | |
| -7 | | | | | | | | | | | | | |
| -8 | | | | | | | | | | | | | |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | | | | | | | | | | | | | |
| Total | | 1 (5%) | 2 (11%) | 4 (21%) | 5 (26%) | 4 (21%) | 2 (11%) | | 1 (5%) | | | | 19 (100%) |

Year 5

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | 2 | 1 | | | | | | 3 (18%) |
| 1 | | | | | | | | | 1 | | | | 1 (6%) |
| 0 | | | | | | | 1 | | | | | | 1 (6%) |
| -1 | | 1 | | | 1 | | | | | | | | 2 (12%) |
| -2 | | | | 2 | 1 | | | | | | | | 3 (18%) |
| -3 | | | 1 | | 1 | 1 | | | | | | | 3 (18%) |
| -4 | | | 1 | 1 | | | | | | | | | 2 (12%) |
| -5 | | | | | | | | | | | | | |
| -6 | | | | 1 | | | | | | | | | 1 (6%) |
| -7 | | | | | 1 | | | | | | | | 1 (6%) |
| -8 | | | | | | | | | | | | | |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | | | | | | | | | | | | | |
| Total | | 1 (6%) | 2 (12%) | 4 (24%) | 4 (24%) | 3 (18%) | 2 (12%) | | 1 (6%) | | | | 17 (100%) |

Year 6

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 1 | | | | | | | 1 | | | | | | 1 (6%) |
| 0 | | | | | | 1 | 1 | | 1 | | | | 3 (19%) |
| -1 | | | | | 1 | 1 | | | | | | | 2 (13%) |
| -2 | | | | | | | | | | | | | |
| -3 | | 1 | | 1 | 1 | 1 | | | | | | | 4 (25%) |
| -4 | | | | | 1 | | | | | | | | 1 (6%) |
| -5 | | | | 1 | | | | | | | | | 1 (6%) |
| -6 | | | 2 | 1 | | | | | | | | | 3 (19%) |
| -7 | | | | | | | | | | | | | |
| -8 | | | | | 1 | | | | | | | | 1 (6%) |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | | | | | | | | | | | | | |
| Total | | 1 (6%) | 2 (13%) | 3 (19%) | 4 (25%) | 3 (19%) | 2 (13%) | | 1 (6%) | | | | 16 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure.

**Figure 8: Change in CLN2-MLVS clinical rating scale score (1:1 matched NH); Year 1 to 3**

Year 1

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | |
| 0 | 1 | | 1 | 1 | | | | | 1 | | | | 4 (11%) |
| -1 | 1 | 1 | | | 3 | 1 | 1 | 2 | 1 | | | | 10 (26%) |
| -2 | | | | | | | | | 1 | | | | 1 (3%) |
| -3 | 2 | 2 | | 1 | | 2 | 2 | | | | | | 9 (24%) |
| -4 | 1 | | 1 | 1 | | | 1 | | | | | | 4 (11%) |
| -5 | 2 | | | | 1 | 2 | | | | | | | 5 (13%) |
| -6 | | | | 1 | 4 | | | | | | | | 5 (13%) |
| -7 | | | | | | | | | | | | | |
| -8 | | | | | | | | | | | | | |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | | | | | | | | | | | | | |
| Total | 7 (18%) | 3 (8%) | 2 (5%) | 4 (11%) | 8 (21%) | 5 (13%) | 4 (11%) | 2 (5%) | 3 (8%) | | | | 38 (100%) |

Year 2

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | |
| 0 | | | | 1 | | | | | | | | | 1 (5%) |
| -1 | | | | | | | | | 2 | | | | 2 (9%) |
| -2 | | 1 | | | | 1 | | | | | | | 2 (9%) |
| -3 | | | | | | | | | | | | | |
| -4 | | | | | | | | 1 | | | | | 1 (5%) |
| -5 | 2 | | | | 1 | | 1 | | | | | | 4 (18%) |
| -6 | | | | | 3 | 2 | | | | | | | |
| -7 | 1 | | | 1 | | | | | | | | | 5 (23%) |
| -8 | 2 | | | 2 | | | | | | | | | 2 (9%) |
| -9 | | | | | | | | | | | | | 4 (18%) |
| -10 | | | | | | | | | | | | | |
| -11 | 1 | | | | | | | | | | | | 1 (5%) |
| -12 | | | | | | | | | | | | | |
| Total | 6 (27%) | 1 (5%) | | 4 (18%) | 4 (18%) | 3 (14%) | 1 (5%) | 1 (5%) | 2 (9%) | | | | 22 (100%) |

Year 3

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | | |
| -1 | | | | | | | | | | | | | |
| -2 | | | | 1 | | | | | 2 | | | | 3 (16%) |
| -3 | | | | | | | 1 | 1 | | | | | 2 (11%) |
| -4 | | | | | | | | | 1 | | | | 1 (5%) |
| -5 | 1 | | | | | | | | | | | | 1 (5%) |
| -6 | | 1 | | | 3 | 1 | | | | | | | 5 (26%) |
| -7 | | | | | 1 | 1 | | | | | | | 2 (11%) |
| -8 | 1 | | | 1 | | | | | | | | | 2 (11%) |
| -9 | | | | | | | | | | | | | |
| -10 | 1 | | | | | | | | | | | | 1 (5%) |
| -11 | | | | | | | | | | | | | |
| -12 | 2 | | | | | | | | | | | | 2 (11%) |
| Total | 5 (26%) | 1 (5%) | | 2 (11%) | 4 (21%) | 2 (11%) | 1 (5%) | 1 (5%) | 3 (16%) | | | | 19 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history.

**Figure 9: Change in CLN2-MLVS clinical rating scale score (1:1 matched NH); Year 4 to 6**

Year 4

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | | |
| -1 | | | | | | | | | 1 | | | | 1 (20%) |
| -2 | | | | | | | | | | | | | |
| -3 | | | | | | | | | | | | | |
| -4 | | | | | | | | | | | | | |
| -5 | | | | | | | | | | | | | |
| -6 | | | | | | | | | | | | | |
| -7 | | | | | 1 | 1 | | | | | | | 2 (40%) |
| -8 | | | | | 1 | | | | | | | | 1 (20%) |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | 1 | | | | | | | | | | | | 1 (20%) |
| Total | 1 (20%) | | | | 2 (40%) | 1 (20%) | | | 1 (20%) | | | | 5 (100%) |

Year 5

Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | | |
| -1 | | | | | | | | | | | | | |
| -2 | | | | | | | | | | | | | |
| -3 | | | | | | | | | | | | | |
| -4 | | | | | | | | | | | | | |
| -5 | | | | | | | 1 | | | | | | 1 (33%) |
| -6 | | | | | | | | | | | | | |
| -7 | | | | | | | | | | | | | |
| -8 | | | | | 1 | | | | | | | | 1 (33%) |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | 1 | | | | | | | | | | | | 1 (33%) |
| Total | 1 (33%) | | | | 1 (33%) | | 1 (33%) | | | | | | 3 (100%) |

Year 6

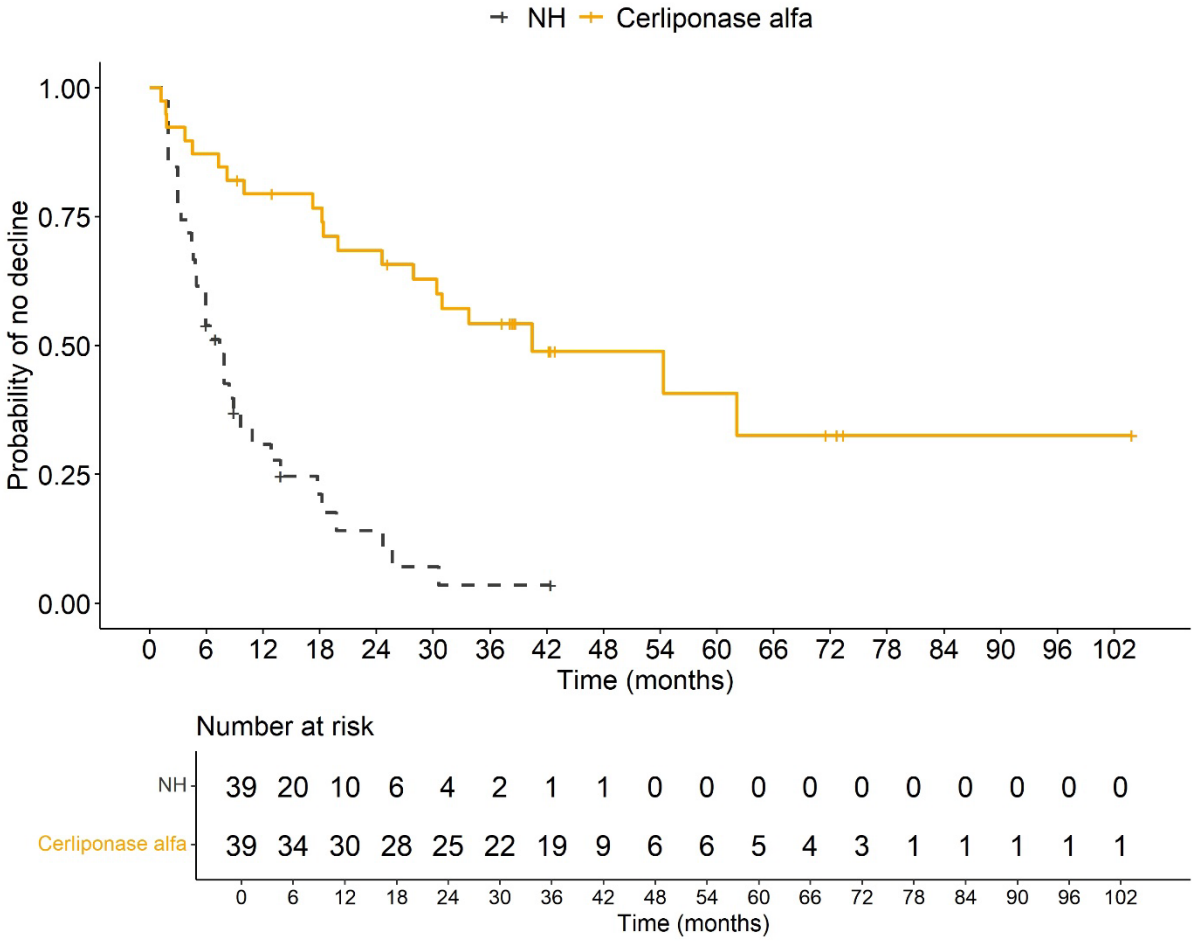
Baseline CLN2-MLVS clinical rating scale score

| Change in CLN2-MLVS clinical rating scale score | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | | |
| -1 | | | | | | | | | | | | | |
| -2 | | | | | | | | | | | | | |
| -3 | | | | | | | | | | | | | |
| -4 | | | | | | | | | | | | | |
| -5 | | | | | | | | | | | | | |
| -6 | | | | | | | | | | | | | |
| -7 | | | | | | 1 | | | | | | | 1 (33%) |
| -8 | | | | | 1 | | | | | | | | 1 (33%) |
| -9 | | | | | | | | | | | | | |
| -10 | | | | | | | | | | | | | |
| -11 | | | | | | | | | | | | | |
| -12 | 1 | | | | | | | | | | | | 1 (33%) |
| Total | 1 (33%) | | | | 1 (33%) | 1 (33%) | | | | | | | 3 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history.

The Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-MLVS score or score of zero and summary are shown in **Figure 10** and Table 5, respectively. One natural history patient and the corresponding matched patient from the 'all patients' dataset were excluded from the analysis, as that natural history patient had only one MLVS observation.

**Figure 10: Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-MLVS score or score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history.

**Table 5: Kaplan-Meier curve summary for time to unreversed 2-point decline in CLN2-MLVS score or score of zero (1:1 matched NH and 'all patients')**

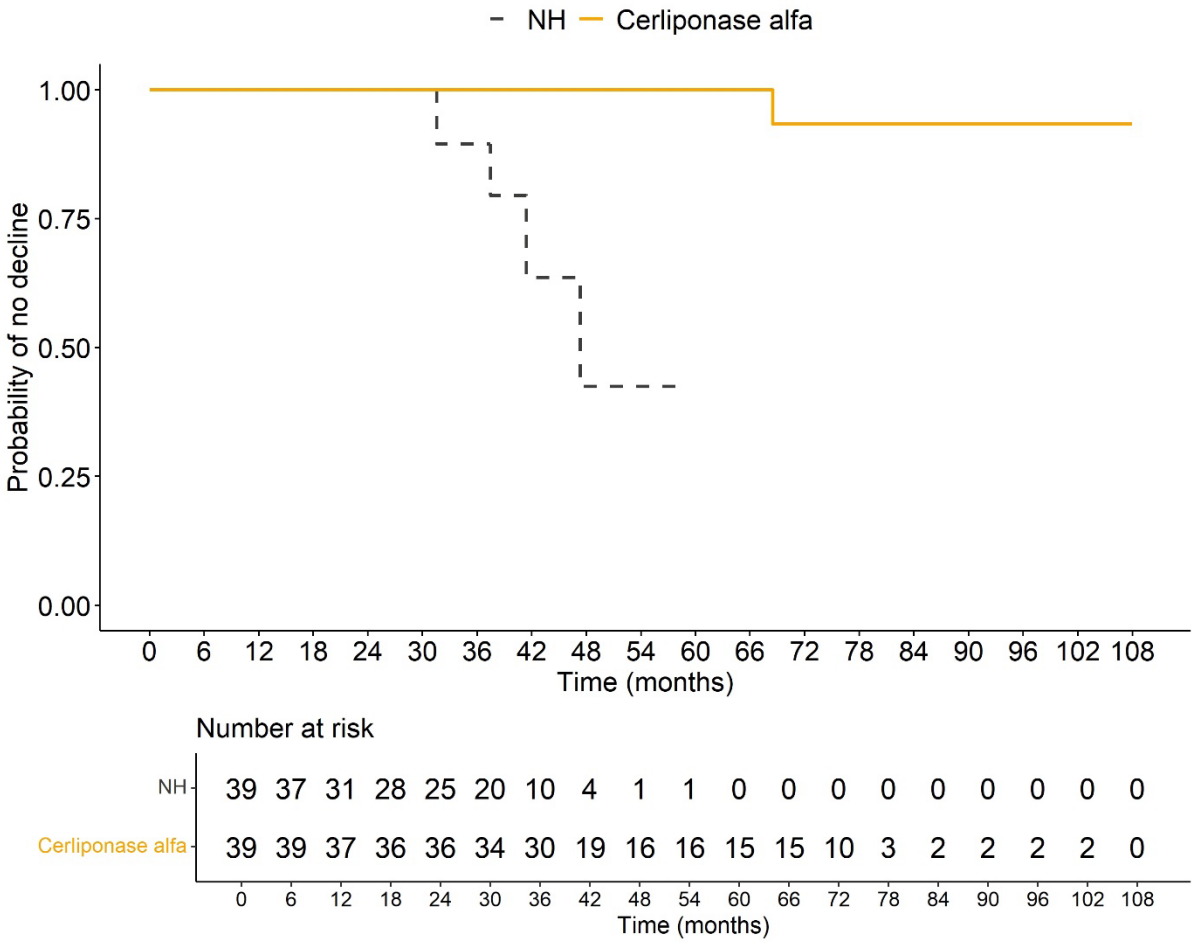
| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 39 | 20 | 40.4 (24.6, NR) | 0.170 (0.089, 0.322) | <0.0001 |
| NH | 39 | 34 | 7.4 (4.6, 9.6) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history; NR, not reached.

The Kaplan-Meier curve for time to CLN2-MLVS score of zero and summary are shown in Figure 11 and Table 6, respectively. One natural history patient and the corresponding

matched patient from the ‘all patients’ dataset were excluded from the analysis, as that natural history patient only had one MLVS observation.

**Figure 11: Kaplan-Meier curve for time to CLN2-MLVS score of zero (1:1 matched NH and ‘all patients’)**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history.

**Table 6: Kaplan-Meier curve summary for time to CLN2-MLVS score of zero (1:1 matched NH and ‘all patients’)**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 39 | 1 | NR (NR, NR) | NE (NE, NE) | NE |
| NH | 39 | 5 | 47.3 (37.5, NR) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history; NE, non-evaluable; NR, not reached.

Table 7 presents the analysis of rate of decline in CLN2-MLVS score of the matched natural history patients and cerliponase ‘all patients’ at 48 weeks. One natural history patient and the corresponding matched patient from the ‘all patients’ dataset were excluded from the analysis, as that natural history patient had only one MLVS observation.

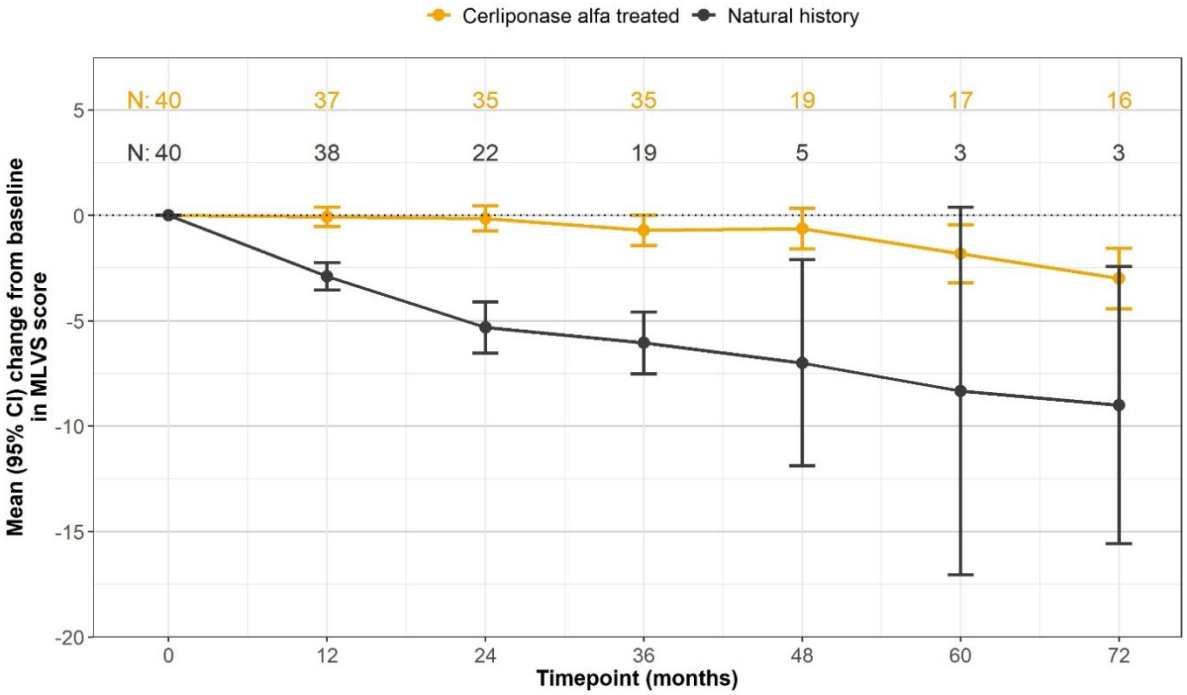
**Table 7: CLN2-MLVS scale – Rate of decline (1:1 matched NH and 'all patients')**

| Rate of Decline (Points/48 weeks) | NH | 'All patients' | Difference (NH–'all patients') | Two-sided p-value |
|---|---|---|---|---|
| MLVS total score | | | | |
| n | 39 | 39 | | |
| Mean (SD) | 2.12 (1.44) | 0.39 (1.03) | 1.73 | <0.0001 |
| (SE) | | | 0.28 | |
| Median | 1.86 | 0.31 | | |
| 25th, 75th Percentile | 1.03, 3.19 | 0, 0.78 | | |
| Min, Max | 0, 7.43 | –2.56, 4.87 | | |
| 95% CI | 1.65, 2.59 | 0.05, 0.72 | 1.17, 2.30 | |

Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history.

Using the same time windows as in Table 1, the change from baseline in CLN2-MLVS score at each year of follow-up is shown in Figure 12.

**Figure 12: Change from baseline in CLN2-MLVS score by year of follow-up (1:1 matched NH and 'all patients')**




Abbreviations: Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; MLVS, motor language vision seizure; NH, natural history.

### CLN2-M clinical rating scale score

Using the same time windows as in Table 1, the number and percentage of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline at each year of follow-up is presented in Figure 13 and Figure 14 for the cerliponase alfa 'all patients' and the matched natural history dataset, respectively.

**Figure 13: Change in CLN2-M clinical rating scale score – (1:1 matched 'all patients')**

Year 1

Change in CLN2-M clinical rating scale score

| | Baseline CLN2-M clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | 1 | 1 | | 2 (5%) |
| 0 | 9 | 10 | 6 | | 25 (68%) |
| -1 | | 8 | 1 | | 9 (24%) |
| -2 | 1 | | | | 1 (3%) |
| -3 | | | | | |
| Total | 10 (27%) | 19 (51%) | 8 (22%) | | 37 (100%) |

Year 2

Change in CLN2-M clinical rating scale score

| | Baseline CLN2-M clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | 1 | | | 1 (3%) |
| 0 | 8 | 8 | 7 | | 23 (66%) |
| -1 | | 11 | | | 11 (31%) |
| -2 | | | | | |
| -3 | | | | | |
| Total | 8 (23%) | 20 (57%) | 7 (20%) | | 35 (100%) |

Year 3

Change in CLN2-M clinical rating scale score

| | Baseline CLN2-M clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 6 | 7 | 9 | | 22 (63%) |
| -1 | 1 | 11 | | | 12 (34%) |
| -2 | | 1 | | | 1 (3%) |
| -3 | | | | | |
| Total | 7 (20%) | 19 (54%) | 9 (26%) | | 35 (100%) |

Year 4

Change in CLN2-M clinical rating scale score

| | Baseline CLN2-M clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 1 | 4 | 5 | | 10 (53%) |
| -1 | | 8 | 1 | | 9 (47%) |
| -2 | | | | | |
| -3 | | | | | |
| Total | 1 (5%) | 12 (63%) | 6 (32%) | | 19 (100%) |

Year 5

Change in CLN2-M clinical rating scale score

| | Baseline CLN2-M clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | 2 | 2 | | 4 (24%) |
| -1 | 1 | 9 | 2 | | 12 (71%) |
| -2 | | 1 | | | 1 (6%) |
| -3 | | | | | |
| Total | 1 (6%) | 12 (71%) | 4 (24%) | | 17 (100%) |

Year 6

Change in CLN2-M clinical rating scale score

| | Baseline CLN2-M clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | 1 | 2 | | 3 (19%) |
| -1 | | 9 | 2 | | 11 (69%) |
| -2 | 1 | 1 | | | 2 (13%) |
| -3 | | | | | |
| Total | 1 (6%) | 11 (69%) | 4 (25%) | | 16 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; M, motor.

**Figure 14: Change in CLN2-M clinical rating scale score – (1:1 matched NH)**

Year 1

Change in CLN2-M clinical rating scale score | Baseline CLN2-M clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 3 | 3 | 2 | | 8 (21%) |
| -1 | 7 | 4 | 6 | | 17 (44%) |
| -2 | 1 | 12 | | | 13 (33%) |
| -3 | 1 | | | | 1 (3%) |
| Total | 12 (31%) | 19 (49%) | 8 (21%) | | 39 (100%) |

Year 2

Change in CLN2-M clinical rating scale score | Baseline CLN2-M clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | 1 | | | 1 (4%) |
| -1 | 4 | 2 | 4 | | 10 (40%) |
| -2 | 1 | 10 | | | 11 (44%) |
| -3 | 3 | | | | 3 (12%) |
| Total | 8 (32%) | 13 (52%) | 4 (16%) | | 25 (100%) |

Year 3

Change in CLN2-M clinical rating scale score | Baseline CLN2-M clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | 1 | 7 | | 8 (40%) |
| -2 | 1 | 6 | | | 7 (35%) |
| -3 | 5 | | | | 5 (25%) |
| Total | 6 (30%) | 7 (35%) | 7 (35%) | | 20 (100%) |

Year 4

Change in CLN2-M clinical rating scale score | Baseline CLN2-M clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | | 2 | | 2 (40%) |
| -2 | | 2 | | | 2 (40%) |
| -3 | 1 | | | | 1 (20%) |
| Total | 1 (20%) | 2 (40%) | 2 (40%) | | 5 (100%) |

Year 5

Change in CLN2-M clinical rating scale score | Baseline CLN2-M clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | | | | |
| -2 | | 3 | | | 3 (75%) |
| -3 | 1 | | | | 1 (25%) |
| Total | 1 (25%) | 3 (75%) | | | 4 (100%) |

Year 6

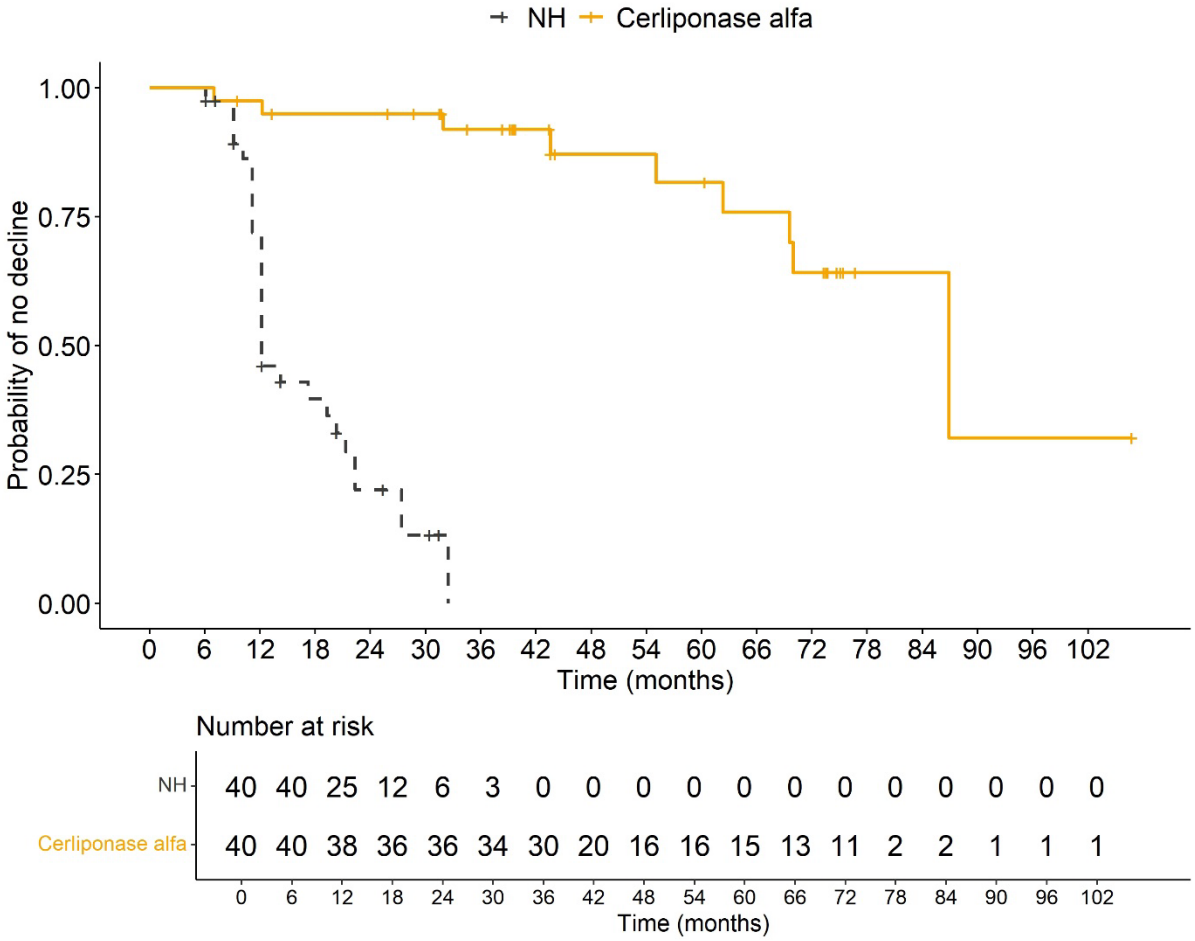
Change in CLN2-M clinical rating scale score | Baseline CLN2-M clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | | 2 | | 2 (50%) |
| -2 | | 1 | | | 1 (25%) |
| -3 | 1 | | | | 1 (25%) |
| Total | 1 (25%) | 1 (25%) | 2 (50%) | | 4 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; M, motor; NH, natural history.

The Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-M score or score of zero and summary are shown in **Figure 15** and Table 8, respectively.

**Figure 15: Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-M score or score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; M, motor; NH, natural history.

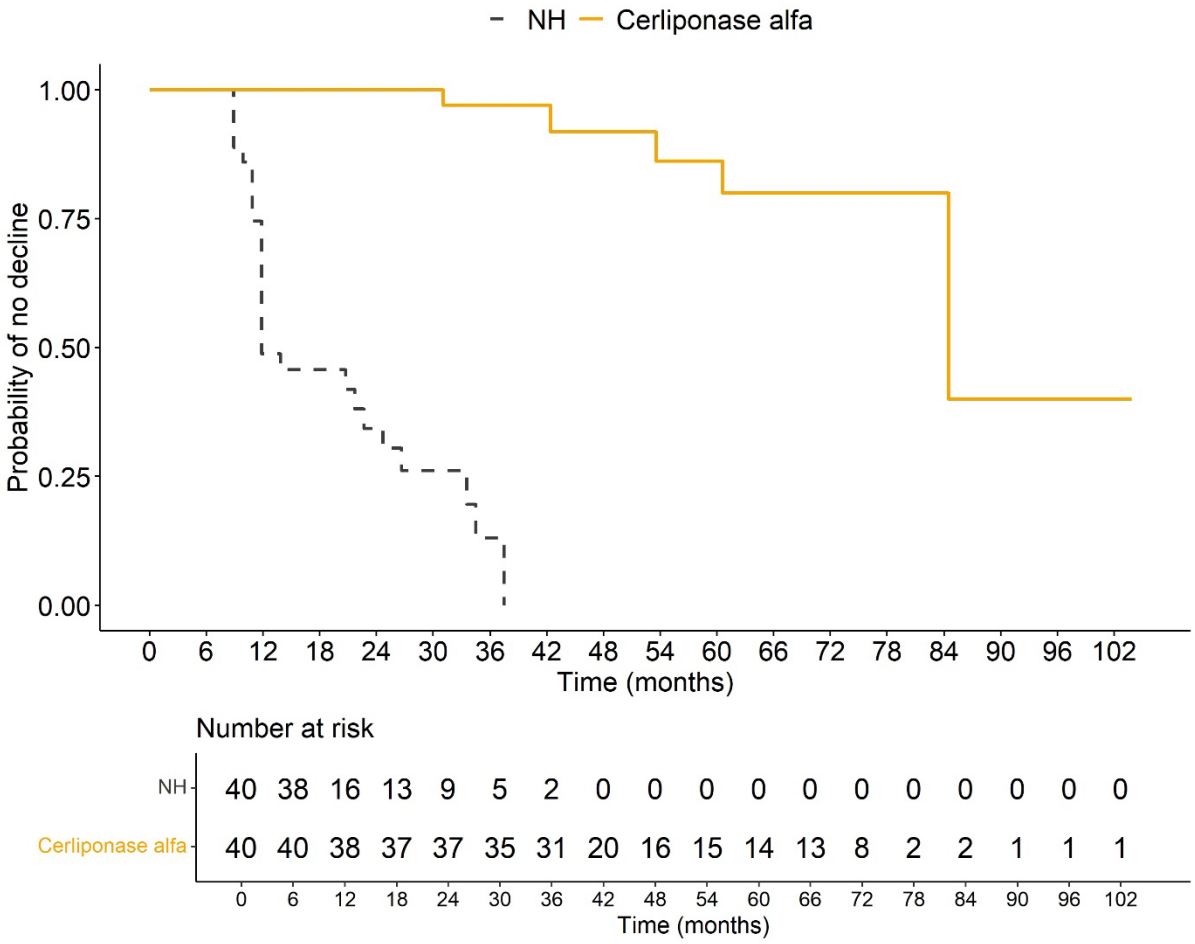
**Table 8: Kaplan-Meier curve summary for time to unreversed 2-point decline in CLN2-M score or score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 9 | 86.9 (69.6, NR) | 0.023 (0.006, 0.089) | <0.0001 |
| NH | 40 | 29 | 12.2 (12.2, 20.3) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; M, motor; NH, natural history; NR, not reached.

The Kaplan-Meier curve for time to CLN2-M score of zero and summary are shown in Figure 16 and Table 9, respectively.

**Figure 16: Kaplan-Meier curve for time to CLN2-M score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; M, motor; NH, natural history.

**Table 9: Kaplan-Meier curve summary for time to CLN2-M score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 5 | 84.5 (84.5, NR) | 0.003 (0.000, 0.031) | <0.0001 |
| NH | 40 | 28 | 11.9 (11.9, 24.7) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; ML, motor; NH, natural history; NR, not reached.

Table 10 presents the analysis of rate of decline in CLN2-M score of the matched natural history patients and cerliponase 'all patients' at 48 weeks.

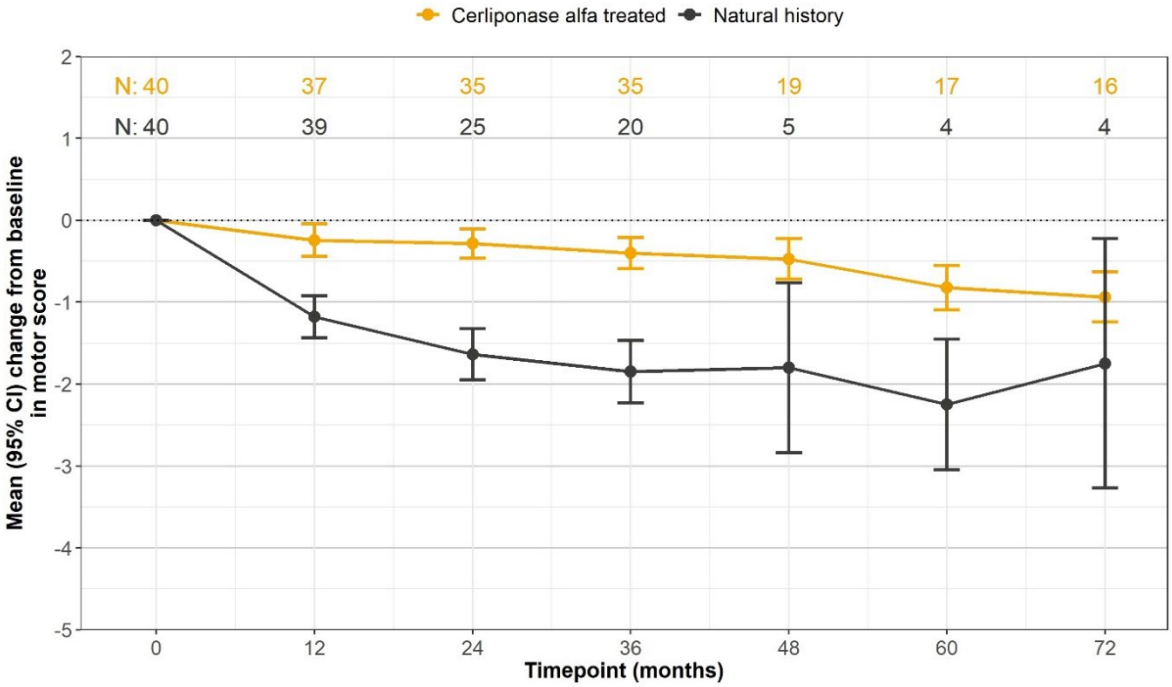
**Table 10: CLN2-M scale – Rate of decline (1:1 matched NH and 'all patients')**

| Rate of Decline (Points/48 weeks) | NH | 'All patients' | Difference (NH–'all patients') | Two-sided p-value |
|---|---|---|---|---|
| Motor score | | | | |
| n | 40 | 40 | | |
| Mean (SD) | 0.69 (0.48) | 0.19 (0.56) | 0.49 | <0.0001 |
| (SE) | | | 0.12 | |
| Median | 0.62 | 0.15 | | |
| 25th, 75th Percentile | 0.33, 0.91 | 0, 0.27 | | |
| Min, Max | 0, 1.86 | –1.19, 3.25 | | |
| 95% CI | 0.53, 0.84 | 0.01, 0.37 | 0.26, 0.73 | |

Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; M, motor language vision seizure; NH, natural history.

Using the same time windows as in Table 1, the change from baseline in CLN2-M score at each year of follow-up is shown in Figure 17.

**Figure 17: Change from baseline in CLN2-M score by year of follow-up (1:1 matched NH and 'all patients')**




Abbreviations: Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; M, motor; NH, natural history.

### CLN2-L clinical rating scale score

Using the same time windows as in Table 1, the number and percentage of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline at each year of follow-up is presented in Figure 18 and Figure 19 for the cerliponase alfa 'all patients' and the matched natural history dataset, respectively.

**Figure 18: Change in CLN2-L clinical rating scale score – (1:1 matched 'all patients')**

Year 1

| Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | 1 | 1 | 2 (5%) |
| 0 | 8 | 8 | 8 | | 24 (65%) |
| -1 | 2 | 6 | 3 | | 11 (30%) |
| -2 | | | | | |
| -3 | | | | | |
| Total | 10 (27%) | 14 (38%) | 12 (32%) | 1 (3%) | 37 (100%) |

Year 2

| Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | 1 | 1 | 2 (6%) |
| 0 | 8 | 8 | 9 | | 25 (71%) |
| -1 | 1 | 5 | 1 | | 7 (20%) |
| -2 | | 1 | | | 1 (3%) |
| -3 | | | | | |
| Total | 9 (26%) | 14 (40%) | 11 (31%) | 1 (3%) | 35 (100%) |

Year 3

| Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | 2 | 1 | 3 (9%) |
| 0 | 6 | 5 | 7 | | 18 (51%) |
| -1 | 1 | 8 | 3 | | 12 (34%) |
| -2 | | 2 | | | 2 (6%) |
| -3 | | | | | |
| Total | 7 (20%) | 15 (43%) | 12 (34%) | 1 (3%) | 35 (100%) |

Year 4

| Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | 2 | | 2 (11%) |
| 0 | 1 | 3 | 5 | | 9 (47%) |
| -1 | | 4 | 3 | | 7 (37%) |
| -2 | | 1 | | | 1 (5%) |
| -3 | | | | | |
| Total | 1 (5%) | 8 (42%) | 10 (53%) | | 19 (100%) |

Year 5

| Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | 2 | | 2 (12%) |
| 0 | 1 | 1 | 3 | | 5 (29%) |
| -1 | | 4 | 5 | | 9 (53%) |
| -2 | | 1 | | | 1 (6%) |
| -3 | | | | | |
| Total | 1 (6%) | 6 (35%) | 10 (59%) | | 17 (100%) |

Year 6

| Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | 1 | 2 | | 3 (19%) |
| -1 | 1 | 2 | 7 | | 10 (63%) |
| -2 | | 3 | | | 3 (19%) |
| -3 | | | | | |
| Total | 1 (6%) | 6 (38%) | 9 (56%) | | 16 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; L, language.

**Figure 19: Change in CLN2-L clinical rating scale score – (1:1 matched NH)**

Year 1

Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 3 | 4 | 5 | 2 | 14 (36%) |
| -1 | 5 | 6 | 8 | | 19 (49%) |
| -2 | | 6 | | | 6 (15%) |
| -3 | | | | | |
| Total | 8 (21%) | 16 (41%) | 13 (33%) | 2 (5%) | 39 (100%) |

Year 2

Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 1 | 2 | | 2 | 5 (20%) |
| -1 | 1 | | 6 | | 7 (28%) |
| -2 | 3 | 9 | | | 12 (48%) |
| -3 | 1 | | | | 1 (4%) |
| Total | 6 (24%) | 11 (44%) | 6 (24%) | 2 (8%) | 25 (100%) |

Year 3

Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | 2 | 2 (10%) |
| -1 | | 1 | 6 | | 7 (35%) |
| -2 | | 6 | | | 6 (30%) |
| -3 | 5 | | | | 5 (25%) |
| Total | 5 (25%) | 7 (35%) | 6 (20%) | 2 (20%) | 20 (100%) |

Year 4

Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | | 3 | | 3 (60%) |
| -2 | | 1 | | | 1 (20%) |
| -3 | 1 | | | | 1 (20%) |
| Total | 1 (20%) | 1 (20%) | 3 (60%) | | 5 (100%) |

Year 5

Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | | 2 | | 2 (50%) |
| -2 | | 1 | | | 1 (25%) |
| -3 | 1 | | | | 1 (25%) |
| Total | 1 (25%) | 1 (25%) | 2 (50%) | | 4 (100%) |

Year 6

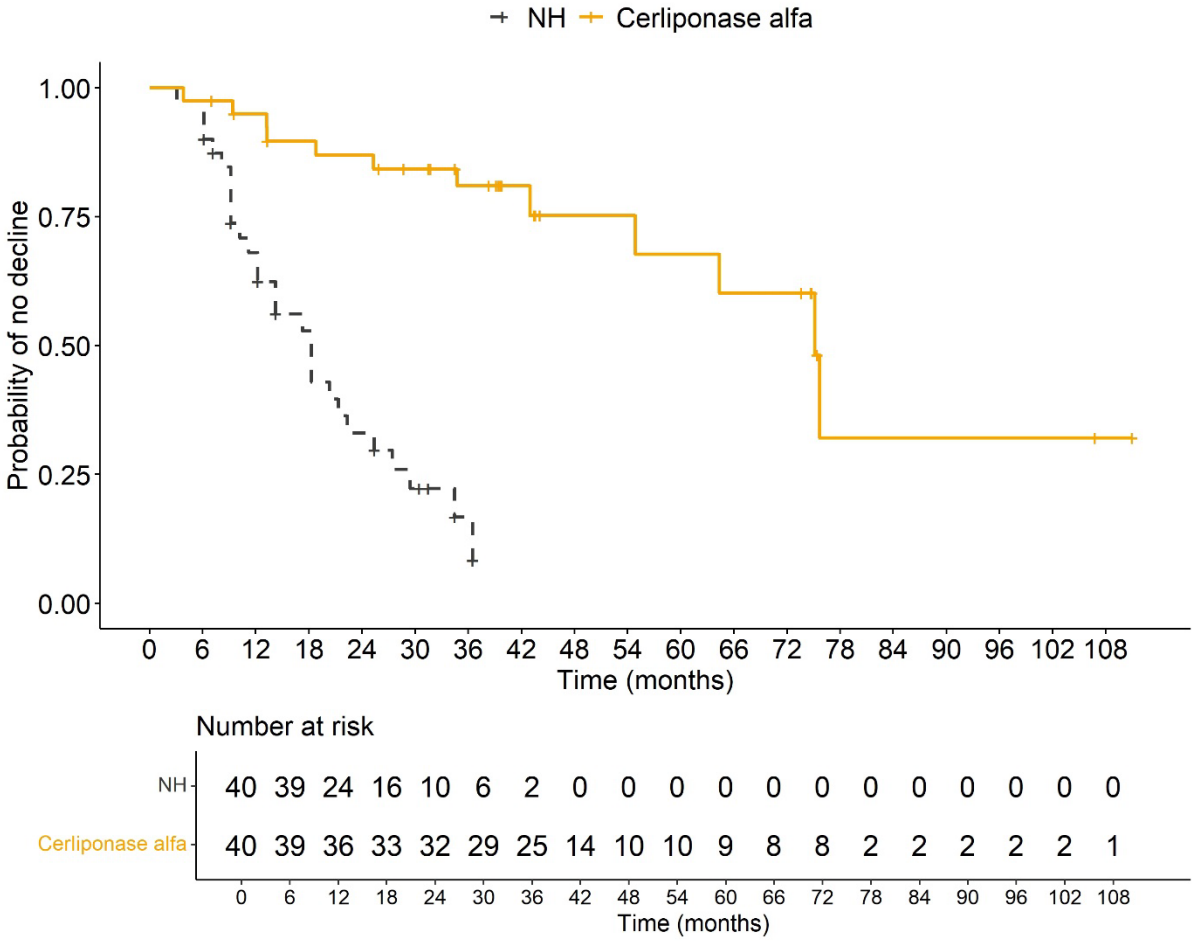
Change in CLN2-L clinical rating scale score | Baseline CLN2-L clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | | 3 | | 3 (75%) |
| -2 | | | | | |
| -3 | 1 | | | | 1 (25%) |
| Total | 1 (25%) | | 3 (75%) | | 4 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; L, language; NH, natural history.

The Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-L score or score of zero and summary are shown in **Figure 20** and Table 11, respectively.

**Figure 20: Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-L score or score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; L, language; NH, natural history.

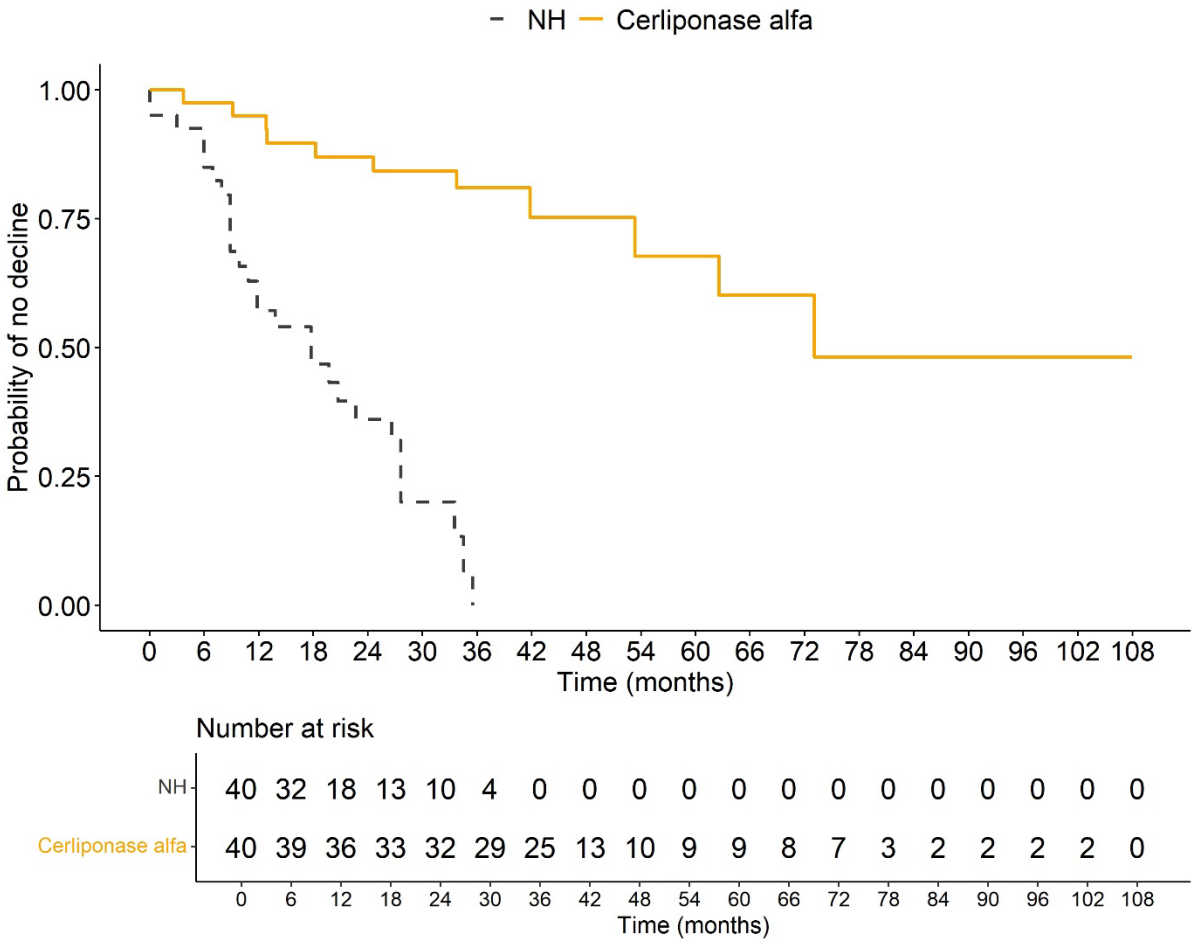
**Table 11: Kaplan-Meier curve summary for time to unreversed 2-point decline in CLN2-L score or score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 12 | 75.1 (54.9, NR) | 0.114 (0.048, 0.271) | <0.0001 |
| NH | 40 | 28 | 18.3 (12.2, 22.3) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; L, language; NH, natural history; NR, not reached.

The Kaplan-Meier curve for time to CLN2-L score of zero and summary are shown in Figure 21 and Table 12, respectively.

**Figure 21: Kaplan-Meier curve for time to CLN2-L score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; L, language; NH, natural history.

**Table 12: Kaplan-Meier curve summary for time to CLN2-L score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 11 | 73.1 (53.4, NR) | 0.049 (0.018, 0.135) | <0.0001 |
| NH | 40 | 29 | 17.8 (9.9, 26.6) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; L, language; NH, natural history; NR, not reached.

Table 13 presents the analysis of rate of decline in CLN2-L score of the matched natural history patients and cerliponase 'all patients' at 48 weeks.

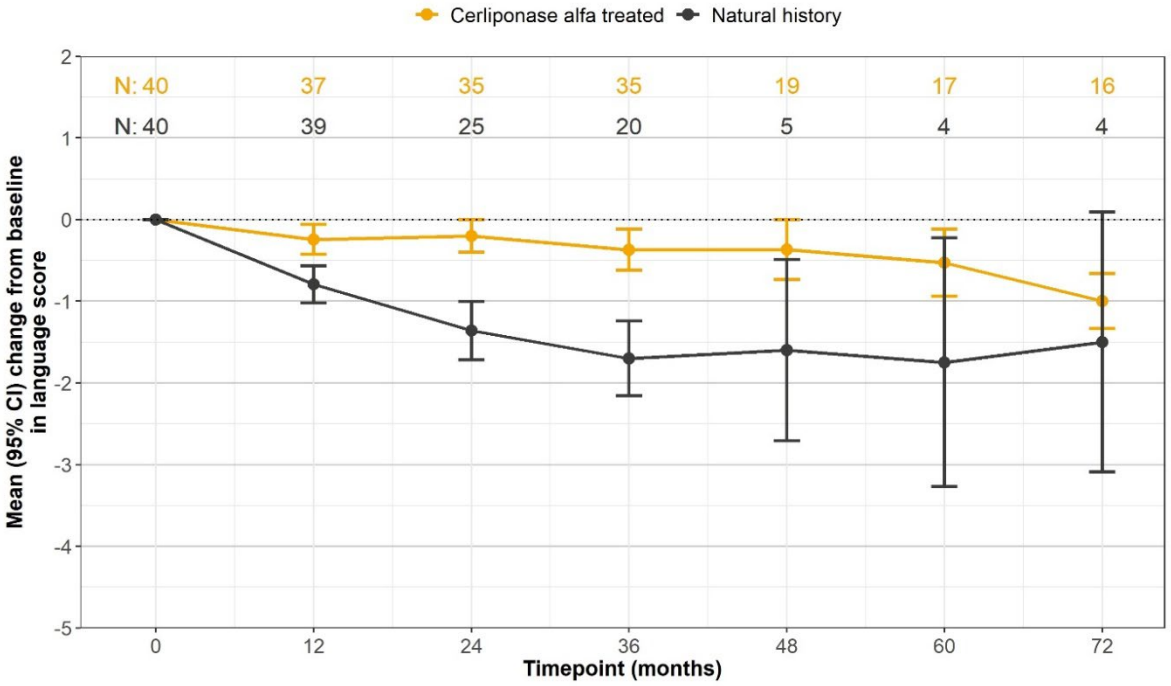
**Table 13: CLN2-L scale – Rate of decline (1:1 matched NH and 'all patients')**

| Rate of Decline (Points/48 weeks) | NH | 'All patients' | Difference (NH–'all patients') | Two-sided p-value |
|---|---|---|---|---|
| Language score | | | | |
| n | 40 | 40 | | |
| Mean (SD) | 0.58 (0.49) | 0.13 (0.17) | 0.45 | <0.0001 |
| (SE) | | | 0.08 | |
| Median | 0.53 | 0.13 | | |
| 25th, 75th Percentile | 0.16, 0.88 | 0, 0.27 | | |
| Min, Max | 0, 1.86 | -0.29, 0.71 | | |
| 95% CI | 0.42, 0.73 | 0.07, 0.18 | 0.29, 0.61 | |

Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; L, language; NH, natural history.

Using the same time windows as in Table 1, the change from baseline in CLN2-L score at each year of follow-up is shown in Figure 22.

**Figure 22: Change from baseline in CLN2-L score by year of follow-up (1:1 matched NH and 'all patients')**




Abbreviations: Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; L, language; NH, natural history.

### CLN2-V clinical rating scale score

Using the same time windows as in Table 1, the number and percentage of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline at each year of follow-up is presented in Figure 23 and Figure 24 for the cerliponase alfa 'all patients' and the matched natural history dataset, respectively.

**Figure 23: Change in CLN2-V clinical rating scale score – (1:1 matched 'all patients')**

Year 1

| Change in CLN2-V clinical rating scale score | Baseline CLN2-V clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | 1 | | | 1 (3%) |
| 0 | 29 | 1 | | | 30 (81%) |
| -1 | 5 | 1 | | | 6 (16%) |
| -2 | | | | | |
| -3 | | | | | |
| Total | 34 (92%) | 3 (8%) | | | 37 (100%) |

Year 2

| Change in CLN2-V clinical rating scale score | Baseline CLN2-V clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | 1 | | | 1 (3%) |
| 0 | 26 | 1 | | | 27 (77%) |
| -1 | 6 | 1 | | | 7 (20%) |
| -2 | | | | | |
| -3 | | | | | |
| Total | 32 (91%) | 3 (8%) | | | 35 (100%) |

Year 3

| Change in CLN2-V clinical rating scale score | Baseline CLN2-V clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 18 | 1 | | | 19 (54%) |
| -1 | 13 | 2 | | | 15 (43%) |
| -2 | 1 | | | | 1 (3%) |
| -3 | | | | | |
| Total | 32 (91%) | 3 (9%) | | | 35 (100%) |

Year 4

| Change in CLN2-V clinical rating scale score | Baseline CLN2-V clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 8 | | | | 8 (42%) |
| -1 | 7 | 2 | | | 9 (47%) |
| -2 | 2 | | | | 2 (11%) |
| -3 | | | | | |
| Total | 17 (89%) | 2 (11%) | | | 19 (100%) |

Year 5

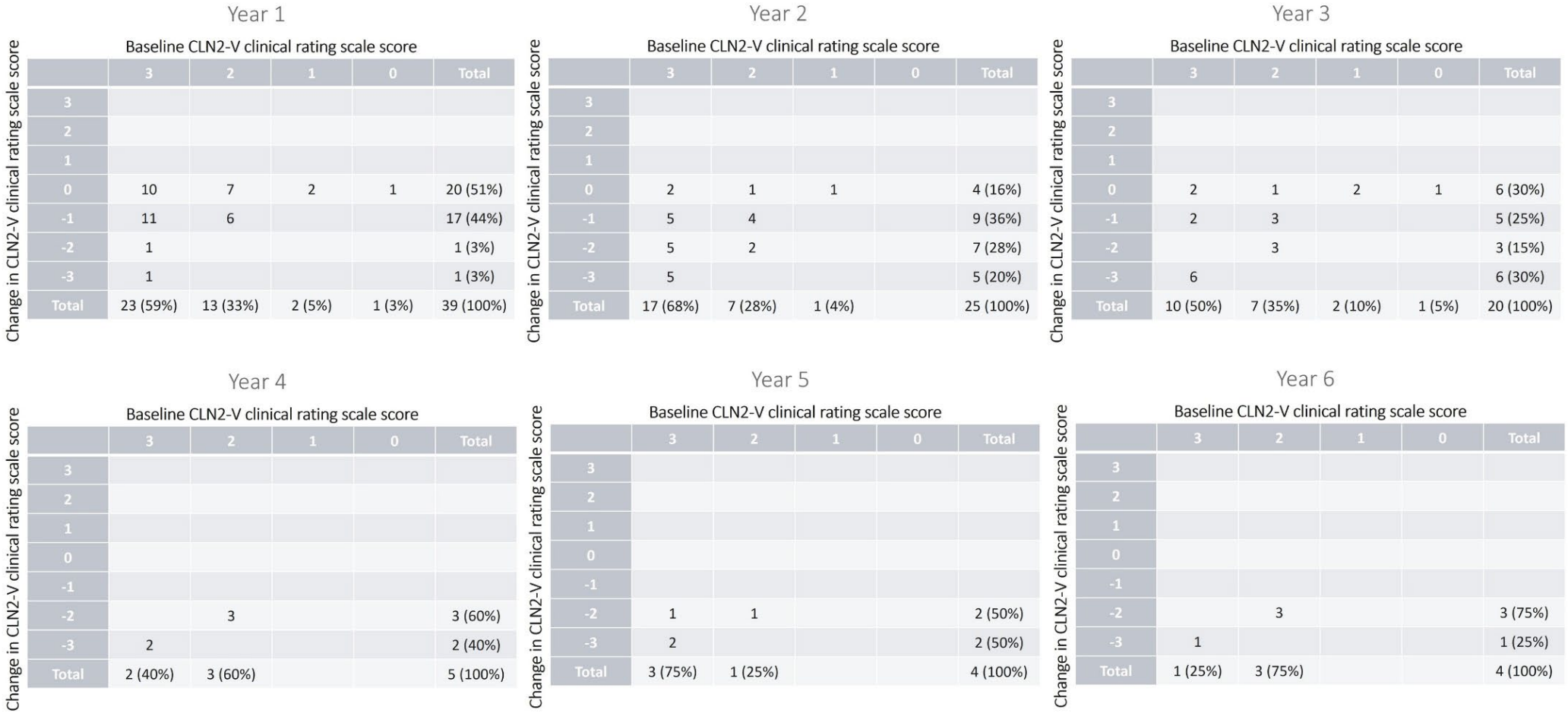
| Change in CLN2-V clinical rating scale score | Baseline CLN2-V clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 3 | | | | 3 (18%) |
| -1 | 7 | 2 | | | 9 (53%) |
| -2 | 3 | | | | 3 (18%) |
| -3 | 2 | | | | 2 (12%) |
| Total | 15 (88%) | 2 (12%) | | | 17 (100%) |

Year 6

| Change in CLN2-V clinical rating scale score | Baseline CLN2-V clinical rating scale score | | | | |
|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | Total |
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | 1 | | | | 1 (6%) |
| -1 | 5 | 2 | | | 7 (44%) |
| -2 | 5 | | | | 5 (31%) |
| -3 | 3 | | | | 3 (19%) |
| Total | 14 (88%) | 2 (13%) | | | 16 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; V, vision.

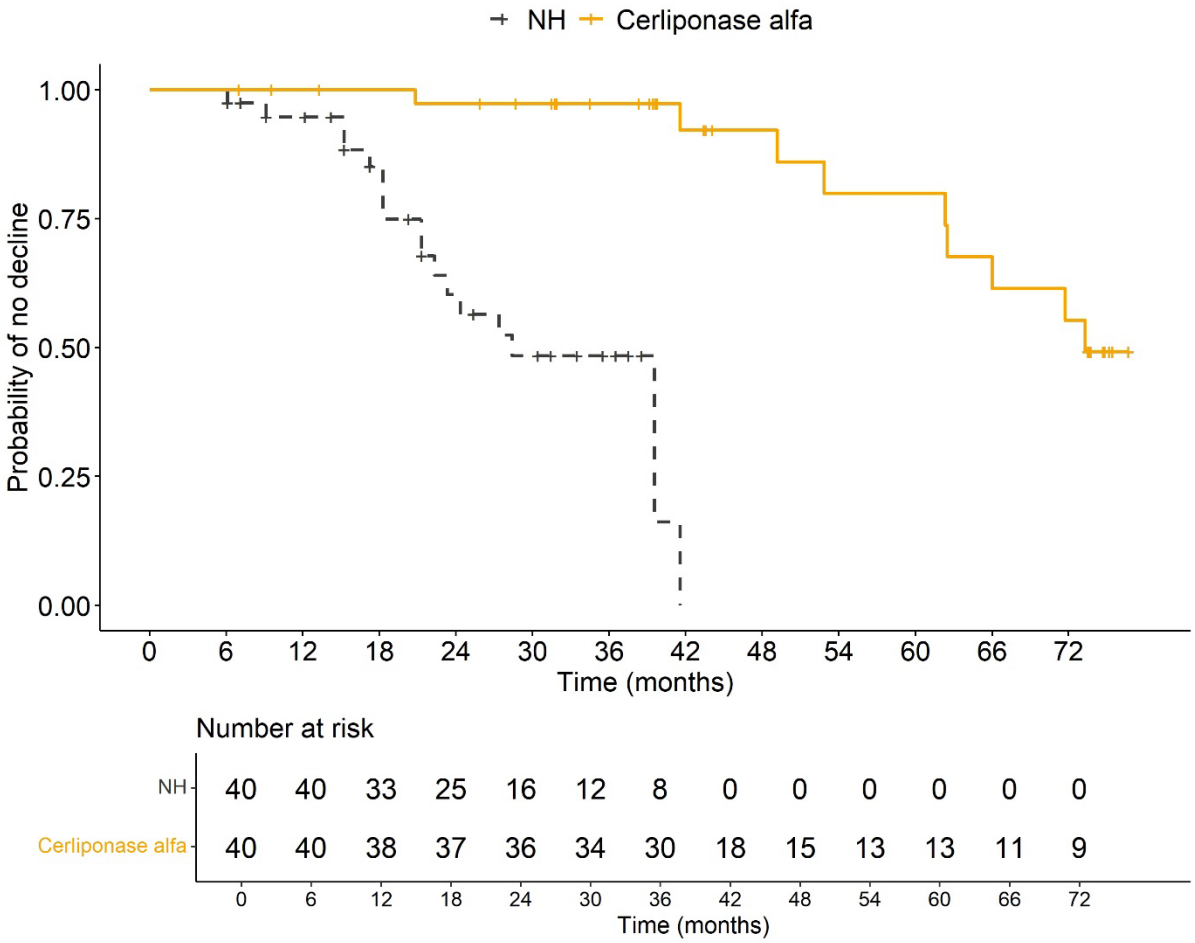
**Figure 24: Change in CLN2-V clinical rating scale score – (1:1 matched NH)**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; V, vision.

The Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-V score or score of zero and summary are shown in **Figure 25** and Table 14, respectively.

**Figure 25: Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-V score or score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; V, vision.

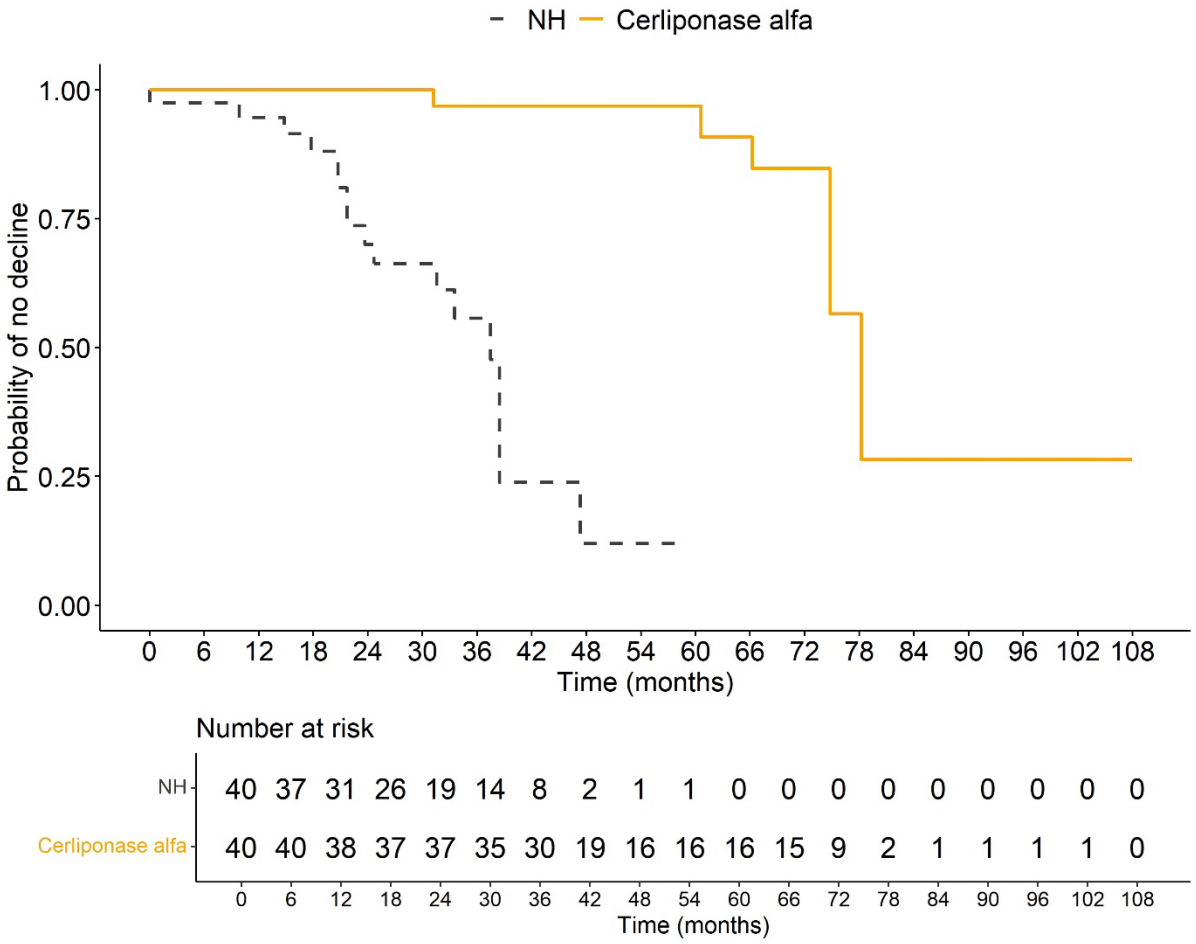
**Table 14: Kaplan-Meier curve summary for time to unreversed 2-point decline in CLN2-V score or score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 9 | 73.3 (62.4, NR) | 0.013 (0.002, 0.072) | <0.0001 |
| NH | 40 | 18 | 28.4 (21.3, 39.6) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; V, vision; NH, natural history; NR, not reached.

The Kaplan-Meier curve for time to CLN2-V score of zero and summary are shown in Figure 26 and Table 15, respectively.

**Figure 26: Kaplan-Meier curve for time to CLN2-V score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; V, vision.

**Table 15: Kaplan-Meier curve summary for time to CLN2-V score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 40 | 5 | 78.2 (74.8, NR) | 0.008 (0.001, 0.087) | <0.0001 |
| NH | 40 | 16 | 37.5 (23.7, 47.3) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; NR, not reached; V, vision.

Table 16 presents the analysis of rate of decline in CLN2-V score of the matched natural history patients and cerliponase 'all patients' at 48 weeks.

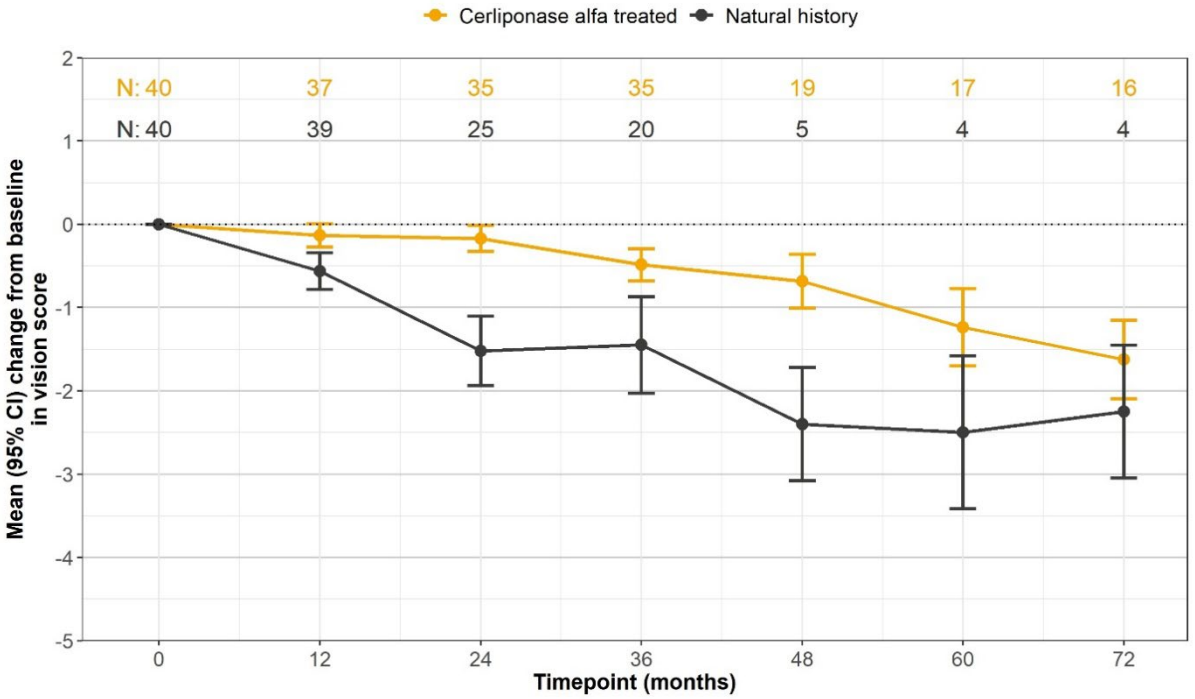
**Table 16: CLN2-V scale – Rate of decline (1:1 matched NH and 'all patients')**

| Rate of Decline (Points/48 weeks) | NH | 'All patients' | Difference (NH–'all patients') | Two-sided p-value |
|---|---|---|---|---|
| Vision score | | | | |
| n | 40 | 40 | | |
| Mean (SD) | 0.55 (0.46) | 0.23 (0.28) | 0.32 | 0.0003 |
| (SE) | | | 0.08 | |
| Median | 0.55 | 0.18 | | |
| 25th, 75th Percentile | 0.23, 0.84 | 0, 0.31 | | |
| Min, Max | 0, 1.86 | 0, 1.62 | | |
| 95% CI | 0.41, 0.70 | 0.14, 0.32 | 0.16, 0.49 | |

Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; V, vision; NH, natural history; V, vision.

Using the same time windows as in Table 1, the change from baseline in CLN2-V score at each year of follow-up is shown in Figure 27.

**Figure 27: Change from baseline in CLN2-V score by year of follow-up (1:1 matched NH and 'all patients')**




Abbreviations: Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; V, vision.

### CLN2-S clinical rating scale score

Using the same time windows as in Table 1, the number and percentage of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline at each year of follow-up is presented in Figure 28 and Figure 29 for the cerliponase alfa 'all patients' and the matched natural history dataset, respectively.

**Figure 28: Change in CLN2-S clinical rating scale score – (1:1 matched 'all patients')**

Year 1

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 4 | 4 (11%) |
| 2 | | | 1 | 1 | 2 (5%) |
| 1 | | 6 | 2 | | 8 (22%) |
| 0 | 15 | 3 | | 2 | 20 (54%) |
| -1 | 2 | | | | 2 (5%) |
| -2 | | 1 | | | 1 (3%) |
| -3 | | | | | |
| Total | 17 (46%) | 10 (27%) | 3 (8%) | 7 (19%) | 37 (100%) |

Year 2

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 4 | 4 (11%) |
| 2 | | | 2 | 1 | 3 (9%) |
| 1 | | 7 | 1 | | 8 (23%) |
| 0 | 13 | 1 | | 1 | 15 (41%) |
| -1 | 3 | | | | 3 (9%) |
| -2 | | 1 | | | 1 (3%) |
| -3 | 1 | | | | 1 (3%) |
| Total | 17 (49%) | 9 (25%) | 3 (9%) | 6 (17%) | 35 (100%) |

Year 3

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 4 | 4 (11%) |
| 2 | | | 3 | 1 | 4 (11%) |
| 1 | | 5 | | 1 | 6 (17%) |
| 0 | 15 | 1 | | | 16 (46%) |
| -1 | 3 | 1 | | | 4 (11%) |
| -2 | | | | | |
| -3 | 1 | | | | 1 (3%) |
| Total | 19 (54%) | 7 (20%) | 3 (9%) | 6 (17%) | 35 (100%) |

Year 4

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 3 | 3 (16%) |
| 2 | | | 1 | 2 | 3 (16%) |
| 1 | | 3 | 1 | | 4 (21%) |
| 0 | 8 | | | | 8 (42%) |
| -1 | | | | | |
| -2 | | 1 | | | 1 (5%) |
| -3 | | | | | |
| Total | 8 (42%) | 4 (21%) | 2 (11%) | 5 (26%) | 19 (100%) |

Year 5

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 3 | 3 (18%) |
| 2 | | | 2 | | 2 (12%) |
| 1 | | 2 | | 1 | 3 (18%) |
| 0 | 5 | 1 | | | 6 (35%) |
| -1 | 2 | 1 | | | 3 (18%) |
| -2 | | | | | |
| -3 | | | | | |
| Total | 7 (41%) | 4 (24%) | 2 (12%) | 4 (24%) | 17 (100%) |

Year 6

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 3 | 3 (19%) |
| 2 | | | 2 | 1 | 3 (19%) |
| 1 | | 2 | | | 2 (13%) |
| 0 | 2 | 1 | | | 3 (19%) |
| -1 | 3 | | | | 3 (19%) |
| -2 | | 1 | | | 1 (6%) |
| -3 | 1 | | | | 1 (6%) |
| Total | 6 (38%) | 4 (25%) | 2 (13%) | 4 (25%) | 16 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; S, seizure.

**Figure 29: Change in CLN2-S clinical rating scale score – (1:1 matched NH)**

Year 1

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 1 | 1 (3%) |
| 2 | | | 1 | | 1 (3%) |
| 1 | | 2 | 2 | 1 | 5 (13%) |
| 0 | 7 | 4 | 3 | 2 | 16 (42%) |
| -1 | 3 | 1 | 3 | | 7 (18%) |
| -2 | 3 | 2 | | | 5 (13%) |
| -3 | 3 | | | | 3 (8%) |
| Total | 16 (42%) | 9 (24%) | 9 (24%) | 4 (11%) | 38 (100%) |

Year 2

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 1 | 1 (5%) |
| 2 | | | 2 | | 2 (9%) |
| 1 | | | | 2 | 2 (9%) |
| 0 | 2 | | | 1 | 3 (14%) |
| -1 | 1 | 3 | 2 | | 6 (27%) |
| -2 | 2 | 1 | | | 3 (14%) |
| -3 | 5 | | | | 5 (23%) |
| Total | 10 (45%) | 4 (18%) | 4 (18%) | 4 (18%) | 22 (100%) |

Year 3

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | 1 | 1 (5%) |
| 0 | 3 | 2 | 2 | 1 | 8 (42%) |
| -1 | 2 | 1 | | | 3 (16%) |
| -2 | 2 | 1 | | | 3 (16%) |
| -3 | 4 | | | | 4 (21%) |
| Total | 11 (58%) | 4 (21%) | 2 (11%) | 2 (11%) | 19 (100%) |

Year 4

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | 1 | 1 (20%) |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | 1 | | 1 (20%) |
| -1 | | | | | |
| -2 | | | | | |
| -3 | 3 | | | | 3 (60%) |
| Total | 3 (60%) | | 1 (20%) | 1 (20%) | 5 (100%) |

Year 5

Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | 1 | 1 (33%) |
| -1 | | | | | |
| -2 | | | | | |
| -3 | 2 | | | | 2 (67%) |
| Total | 2 (67%) | | | 1 (33%) | 3 (100%) |

Year 6

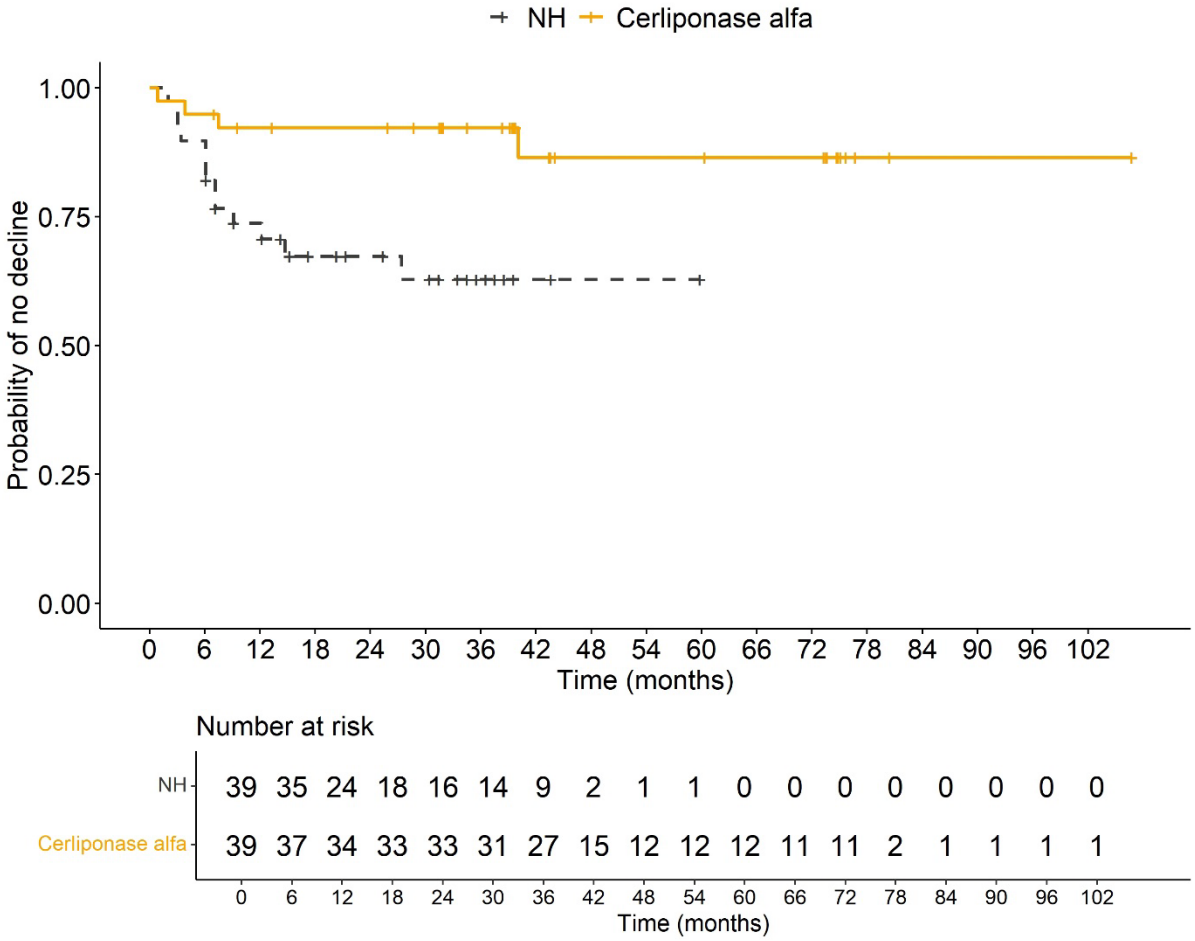
Change in CLN2-S clinical rating scale score | Baseline CLN2-S clinical rating scale score

| | 3 | 2 | 1 | 0 | Total |
|---|---|---|---|---|---|
| 3 | | | | | |
| 2 | | | | | |
| 1 | | | | | |
| 0 | | | | | |
| -1 | | | | | |
| -2 | | | | | |
| -3 | 3 | | | | 3 (100%) |
| Total | 3 (100%) | | | | 3 (100%) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; S, seizure.

The Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-S score or score of zero and summary are shown in **Figure 30** and Table 17, respectively. One natural history patient and the corresponding matched patient from the 'all patients' dataset were excluded from the analysis, as that natural history patient had only one CLN2-S observation.

**Figure 30: Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-S score or score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; S, seizure.

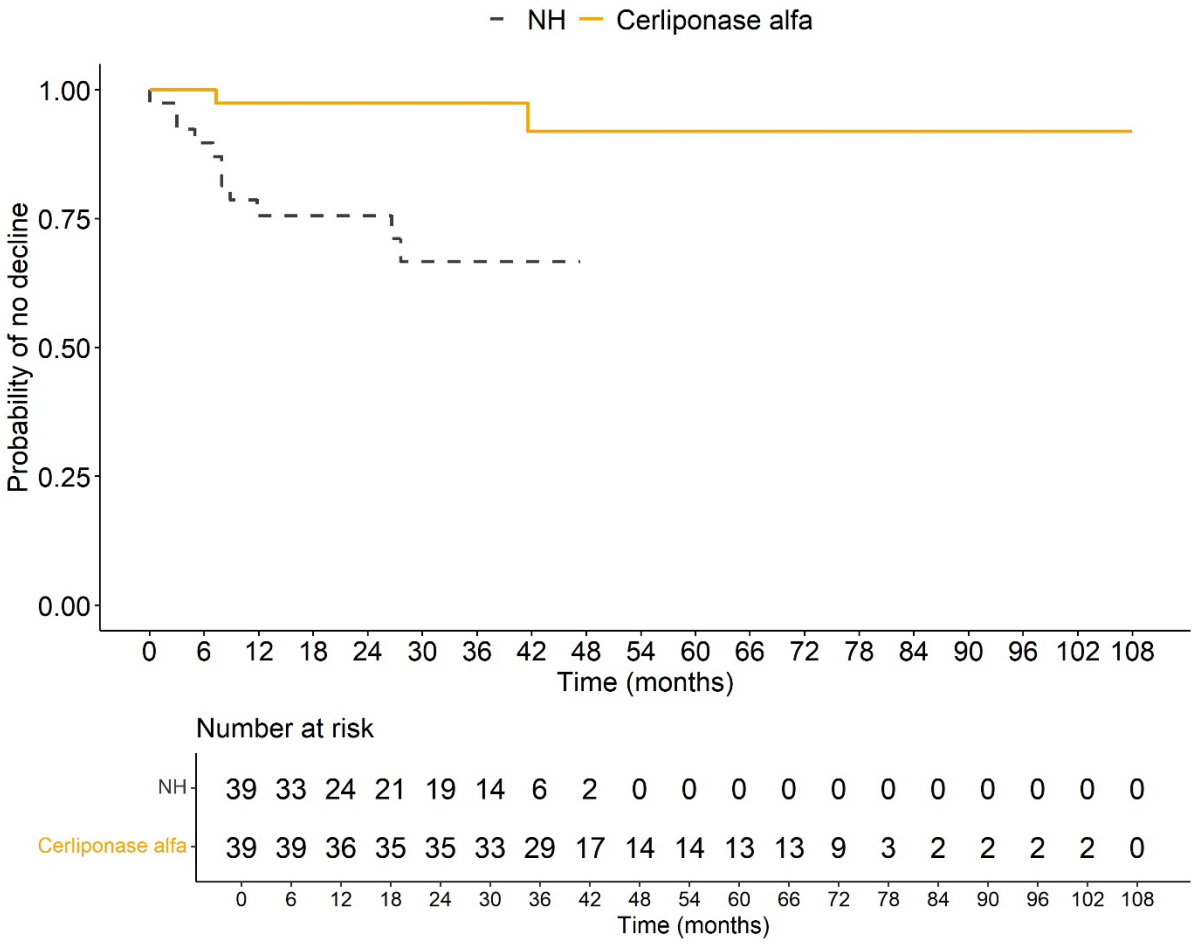
**Table 17:Kaplan-Meier curve summary for time to unreversed 2-point decline in CLN2-S score or score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 39 | 4 | NR (NR, NR) | 0.214 (0.066, 0.695) | 0.010 |
| NH | 39 | 13 | NR (14.7, NR) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; NR, not reached; S, seizure.

The Kaplan-Meier curve for time to CLN2-S score of zero and summary are shown in Figure 31 and Table 18, respectively. One natural history patient and the corresponding matched patient from the 'all patients' dataset were excluded from the analysis, as that natural history patient had only one CLN2-S observation.

**Figure 31: Kaplan-Meier curve for time to CLN2-S score of zero (1:1 matched NH and 'all patients')**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; S, seizure.

**Table 18: Kaplan-Meier curve summary for time to CLN2-S score of zero (1:1 matched NH and 'all patients')**

| Treatment | N | Events | Median | HR (95% CI) Cerliponase alfa vs. NH | p-value |
|---|---|---|---|---|---|
| Cerliponase alfa | 39 | 2 | NR (NR, NR) | 0.106 (0.021, 0.524) | 0.006 |
| NH | 39 | 11 | NR (27.6, NR) | | |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; S, NH, natural history; NR, not reached; seizure.

Table 19 presents the analysis of the rate of decline in CLN2-S score of the matched natural history patients and cerliponase 'all patients' at 48 weeks. One natural history patient and the corresponding matched patient from the 'all patients' dataset were excluded from the analysis, as that natural history patient had only one CLN2-S observation.

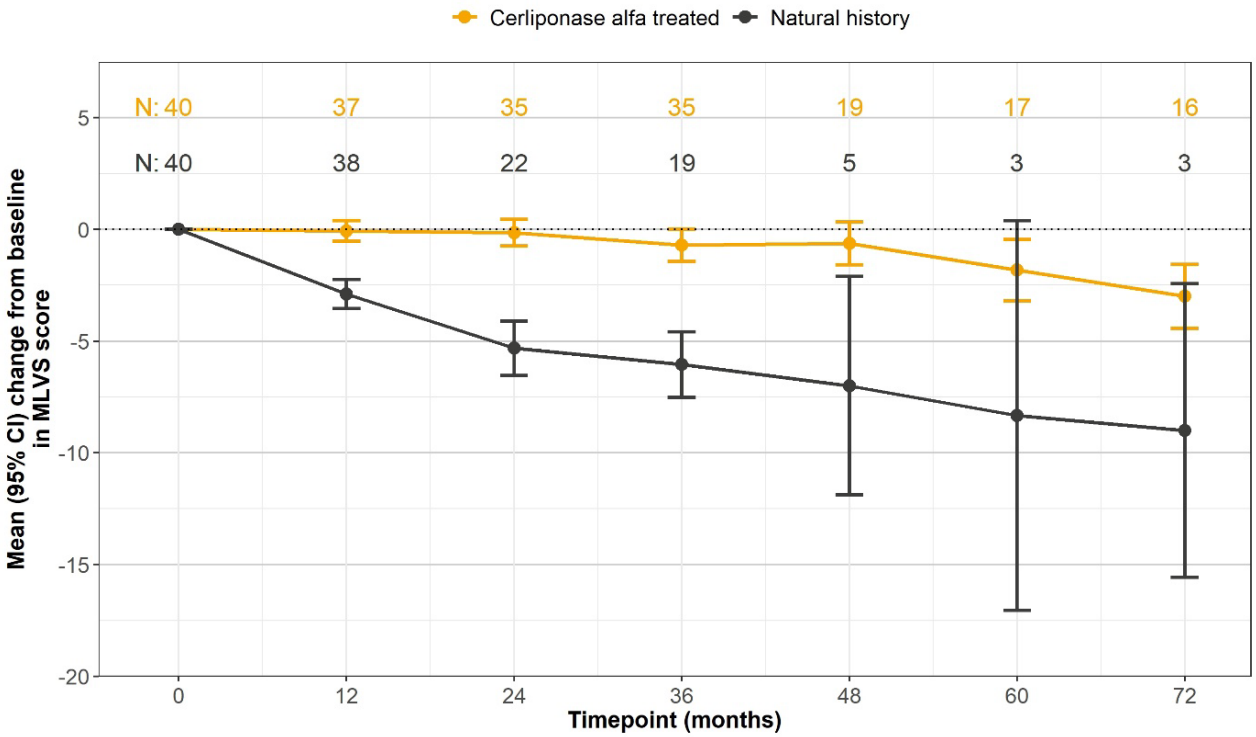
**Table 19: CLN2-S scale – Rate of decline (1:1 matched NH and 'all patients')**

| Rate of Decline (Points/48 weeks) | NH | 'All patients' | Difference (NH–'all patients') | Two-sided p-value |
|---|---|---|---|---|
| Seizure score | | | | |
| n | 39 | 39 | | |
| Mean (SD) | 0.20 (0.62) | -0.17 (0.49) | 0.37 | 0.0050 |
| (SE) | | | 0.13 | |
| Median | 0.00 | 0.00 | | |
| 25th, 75th Percentile | 0.00, 0.48 | -0.31, 0.00 | | |
| Min, Max | -1.12, 1.86 | –2.56, 0.45 | | |
| 95% CI | -0.00, 0.40 | -0.32, -0.01 | 0.11, 0.62 | |

Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; S, seizure.

Using the same time windows as in Table 1, the change from baseline in CLN2-S score at each year of follow-up is shown in Figure 32.

**Figure 32: Change from baseline in CLN2-S score by year of follow-up (1:1 matched NH and 'all patients')**




Abbreviations: Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; NH, natural history; S, seizure.

## *Additional information on included trials*

### A5. Appendix D provides patient disposition data for each study. Please also provide pre-enrolment data for each study, including how many patients were invited to participate but declined (with reasons, if available) and how many were ineligible (with reasons for ineligibility).

An overview of the available pre-enrolment data across the relevant clinical effectiveness studies is outlined in Table 20.

**Table 20: Pre-enrolment information for studies 190-201, 190-202, 190-203, and the MAA**

| | 190-201 | 190-202 | 190-203 | MAA – new starters | MAA – ex-trial |
|---|---|---|---|---|---|
| Patients invited to participate | NR | 24 (all participants from Study 190-201) | NR | 30 | 11 (all surviving English participants from Studies 190-202, 190-203, and 190-502) |
| Declined, n (%) | NR | NA | NR | 1 | 0 |
| Reason(s) for declining | NR | NA | NR | Family decision (n=1) | NA |
| Patients ineligible, n (%) | NR | 1 (4.2%) | NR | 5 | 0 |
| Reason for ineligibility | NR | • Participant withdrew from 190-201 after ICV access device placement and a single infusion of the study drug due to the subject's unwillingness to continue with study procedures | NR | • Participants ineligible due to disease progression (ML score) (n=5) | NA |

Sources: Study 190-202 CSR, 2021 (9); Study 190-203 CSR, 2023 (1); MAA database 2023 (10); Correspondence with treating centres (11).
Abbreviations: ICV, intracerebroventricular infusion; MAA, managed access agreement; NA, not applicable; NR, not reported.

**A6. The submission states that 1:1 matching of untreated patients from Study 190-901 with patients from Study 190-201/202 was performed using key prognostic variables, listed as age, genotype and CLN2 Clinical Rating score).**

**Please provide more details about how these variables were identified and about how different genotypes may affect prognosis**.

The matching algorithm was based on maximising the number of cerliponase alfa treated participants matched to Study 190-901 natural history controls and satisfying several criterial equal baseline ML score, baseline age within 3 months, and genotype (equal number of common alleles [c.622>T, c.509.1G>C]).

- **Equal baseline ML score and baseline age within 3 months**: To facilitate the comparison of cerliponase alfa treated participants to natural history controls with respect to the clinical course of CLN2 disease over time (as represented by the 0–6 point ML score vs time), treated participants were matched to natural history subjects on the basis of study participants' baseline ML scores.

- **Genotype:** Specific disease genotypes do not correlate well with phenotype. However, it has been observed that patients with uncommon disease alleles may have a higher probability of expressing a variable phenotype. Variable presentations typically have a later onset, but subsequently have a predictable loss of function. Attenuated presentations are rare. Therefore, the proportion of patients within a cohort with 2 uncommon mutations is used to classify whether there is potential for clinical variability between cohorts. In general, the uncommon mutations representing both disease alleles were found to be infrequent, occurring in 15% of patients (12).

**Please provide details on the statistical methods used for matching, such as weighting or propensity scoring.**

Both Study 190-202 and the MAA participants were matched to natural history controls based on the 1:1 matching algorithm. Study 190-203 participants were matched based on the 3:1 matching algorithm. For analysis purposes Study 190-203 participants therefore had a weight of one and natural history controls were weighted inversely to the number of matches (1/3, 1/2, 1) and the weights were normalised to the number of natural history controls matched to Study 190-203 participants.

Additional natural history matching information and methodology for studies 190-202 and 190-203 can be found in Appendix 3 of the SAP for both studies 190-202 and 190-203, included in the reference pack.

The MAA participants were matched using the same algorithm as Study 190-202 participants. Due to limited MAA reporting, matching was done based on age close and baseline ML scores only.

### Please describe and justify any changes in matching (such as changes in variables used) since the previous appraisal (HST12).

Table 21 provides an overview of the matching criteria of relevant clinical effectiveness studies. The same matching variables and criteria used in HST12 were employed in studies 190-202 and 190-203. Although matched on equal ML score and age within 3 months, MAA participant genotypic phenotype was not collected and therefore MAA participants could not be matched on this variable.

DEM-CHILD-RX is an external real-world evidence retrospective observational study and not managed by BioMarin. Although this study employed different matching criteria, it provided an external validation of the indirect comparison with natural history controls.

**Table 21: NH matching criteria for relevant clinical effectiveness studies**

| 190-201/202 | 190-203 | MAA | DEM-CHILD-RX |
|---|---|---|---|
| • Equal ML score<br>• Age within 3 months<br>• Genome with equal number of common alleles (c.622C-T, c.509.1G-C) | • Equal ML score<br>• Age within 3 months<br>• Genome with equal number of common alleles (c.622C-T, c.509.1G-C) | • Equal ML score<br>• Age within 3 months | • Equal ML score<br>• Age within 12 months |

Sources: Schulz et al, 2024 (2); Study 190-203 CSR, 2023 (1); DEM-CHILD-RX SAP, 2022 (13).
Abbreviations: MAA, Managed access agreement; ML, motor language; NH, natural history.

### A7. Please state how many patients with atypical CLN2 were included in each study.

In the clinic, clinical judgement is used to determine whether a patient is diagnosed with either classic or atypical CLN2. The number of patients presenting with atypical CLN2 was not collected in studies 190-201, 190-202, 190-203, MAA, 190-901, 190-501, 190-502, and 190-504 (1, 9, 10, 12, 14-17). In DEMCHILD-RX and Study 190-801, 14.0% (3/21) and 16.7% (4/24) of the cerliponase alfa treated participants were recorded as having an atypical phenotype at baseline, respectively (18, 19).

**A8. Has there been any follow-up of patients in study 190-202 since completion in 2020, such as to record mortality or changes in ML score? If there has, please provide a summary of this data. If not, please explain why**.

There was no formalised follow-up conducted for Study 190-202, however seven patients subsequently enrolled in Study 190-504. One of these seven patients passed away. As detailed in Submission Document B, Section B.2.10.1, this patient experienced a treatment-refractory dystonic event which was assessed by the investigator as unrelated to the drug or the intracerebroventricular infusion (ICV) device (17).

**A9. The EAG would appreciate greater clarity on any overlap in patient populations or how patients have moved between the included trials. Please provide further information on this, particularly for trials DEM-CHILD, DEM-CHILD-RX and 190-801.**

A patient flow diagram of patient movement across the presented clinical effectiveness and safety trials is presented in Appendix D, Section D.5.3, Figure 3. The supporting retrospective observational cohort studies (DEM-CHILD-RX and Study 190-801) are not managed by BioMarin and are based on data from the DEM-CHILD registry.

DEM-CHILD is a multicentre, multinational clinical database based in Hamburg, Germany. Of the 74 patients available in the DEM-CHILD database as of February 2015, 41 natural history patients were ultimately included in the evaluable population for this 190-901 supplemental analysis used for matching Study 190-202 and Study 190-203.

Two Study 190-901 participants transitioned into the DEM-CHILD-RX study. The DEM-CHILD-RX dataset includes every patient with the diagnosis of CLN2 disease, that initiated on treatment with cerliponase alfa outside of a trial setting included in the DEM-CHILD registry, and had at least 2 assessments of the CLN2 clinical rating scale as of December 2020 (13). DEMCHILD-RX included 29 participants, of which 24 were evaluable and 21 were 1:1 matched with natural history controls (18).

The ongoing Study 190-801 also includes patients that are enrolled in the DEM-CHILD registry database, who have regular follow-up visits at the University Medical Centre Hamburg-Eppendorf, Germany. Note, the 24 evaluable patients included in DEMCHILD-RX are also enrolled into the Wave 1 analysis of Study 190-801.

## *Managed access agreement cohort*

### A10. Please provide a more detailed baseline characteristics table for the MAA cohort, reporting all the characteristics presented in Table 13 of submission Document B. Please also provide baseline characteristics for the "new starters" subgroup.

Detailed baseline characteristics for the matched MAA cohort are presented in Table 22.

**Table 22: 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, 8.50) | 4.25 (3.33, 8.75) | 4.33 (3.5, 8.5) |
| Sex†, n (%) | | | | |
| Female | 13 (50.0%) | 6 (23.1%) | 9 (52.9%) | 0 (0.0%) |
| Male | 13 (50.0%) | 3 (11.5%) | 8 (47.1%) | 0 (0.0%) |
| Unknown | 0 | 17 (65.4%) | 0 | 17 (100%) |
| Genome | NR | NR | NR | NR |
| Categorical baseline ML score, n (%) | | | | |
| 1 | 1 (3.9%) | 1 (3.9%) | 0 (0.0%) | 0 (0.0%) |
| 2 | 3 (11.5%) | 3 (11.5%) | 2 (11.8%) | 2 (11.8%) |
| 3 | 2 (7.7%) | 2 (7.7%) | 1 (5.9%) | 1 (5.9%) |
| 4 | 12 (46.2%) | 12 (46.2%) | 9 (52.9%) | 9 (52.9%) |
| 5 | 5 (19.2%) | 5 (19.2%) | 3 (17.7%) | 3 (17.7%) |
| 6 | 3 (11.5%) | 3 (11.5%) | 2 (11.8%) | 2 (11.8%) |
| CLN2 motor score | | | | |
| Mean (SD) | 2.04 (0.66) | 1.96 (0.66) | 2.06 (0.66) | 2 (0.61) |
| Median (min, max) | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) |
| CLN2 language score | | | | |
| Mean (SD) | 1.96 (0.72) | 2.04 (0.72) | 2.06 (0.56) | 2.12 (0.60) |
| Median (min, max) | 2 (0, 3) | 2 (0, 3) | 2 (1, 3) | 2 (1, 3) |
| CLN2 ML score | | | | |
| Mean (SD) | 4 (1.26) | 4 (1.26) | 4.12 (1.11) | 4.12 (1.11) |
| Median (min, max) | 4 (1, 6) | 4 (1, 6) | 4 (2, 6) | 4 (2, 6) |
| CLN2 MLVS score | | | | |
| n | 25 | 26 | 17 | 17 |
| Mean (SD) | 8.36 (2.33) | 9.19 (1.47) | 8.59 (2.21) | 9.29 (1.21) |
| Median (min, max) | 9 (3, 12) | 9 (6, 12) | 9 (4, 12) | 9 (7, 11) |
| Age at disease onset†,‡, months | 26 | 4 | 17 | NR |
| n | 36.2 (7.22) | 34 (2.16) | 37.12 (5.43) | NR |
| | 36 (18, 48) | 34.5 (31, 36) | 36 (30, 48) | NR |

| | 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†)** |
| Mean (SD)<br>Median (min, max) | | | | |
| Age of first seizure†, months<br>n<br>Mean (SD)<br>Median (min, max) | <br>26<br>39.27 (8.49)<br>38 (27, 66) | <br>4<br>37.36 (5.07)<br>36.38 (32.33, 44.33) | <br>17<br>40.06 (9.80)<br>39 (27, 66) | <br>NR<br>NR<br>NR |

Source: BioMarin MAA database, 2023 (10).
†Note that sex, age at disease onset, and age at first seizure were variables not captured in the MAA and therefore the data for MAA FAS is sourced from trial data; ‡Defined as age at first symptom.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; L, language; MAA, managed access agreement; M, motor language; ML, motor language; MLVS, motor language vision seizure; NH, natural history; NR, not reported; S, seizure; SD, standard deviation, V, vision.

## A11. Priority question: Given the gaps in Table 15, the EAG has concerns about the possibility of bias in selection of the reported results for the MAA cohort. Please therefore provide results for CLN2 Clinical Rating Scale total score and the visual acuity outcomes (OCT, VEP, ERG).

To alleviate the concern of bias in the selection of the reported results for the MAA cohort, BioMarin would like to confirm the outcomes that were collected in the MAA:

- Patient information: Age commenced on cerliponase alfa, age at start of MAA, age at cerliponase alfa discontinuation, hospital(s) treated/assessed at, MAA consent date, baseline assessment month
- Patient reported outcomes: PedsQL Core Scales (Parent Reports), CLN2-QL, EQ-5D-5L, Date of PRO assessment, Age at PRO assessment
- CLN2 Disease Rating scale: M, L, V, S score, date of assessment
- Weill Cornell Disease Rating Scale: myoclonus score, feeding score, date of assessment
- ECG 12-Lead: Assessment date, presence of abnormality (yes/no), presence of clinically significant abnormality (yes/no), descriptive summary
- EEG: Assessment date, epileptiform activity (yes/no), frequency slowing vs generalised (yes/no), new EEG activity relative to baseline (yes/no), descriptive summary

- Missed infusions: number of missed infusions since previous assessment
- IVT: Age at first and last IVT infusion
- Date of assessment and descriptive summary information were collected for the following outcomes: ERG, OCT, VEP, Bayley Scales of Infant and Toddler Development (3rd Ed), Wechsler Preschool & Primary Scale of Intelligence (4th Ed), Vineland Adaptive Behaviour Scales

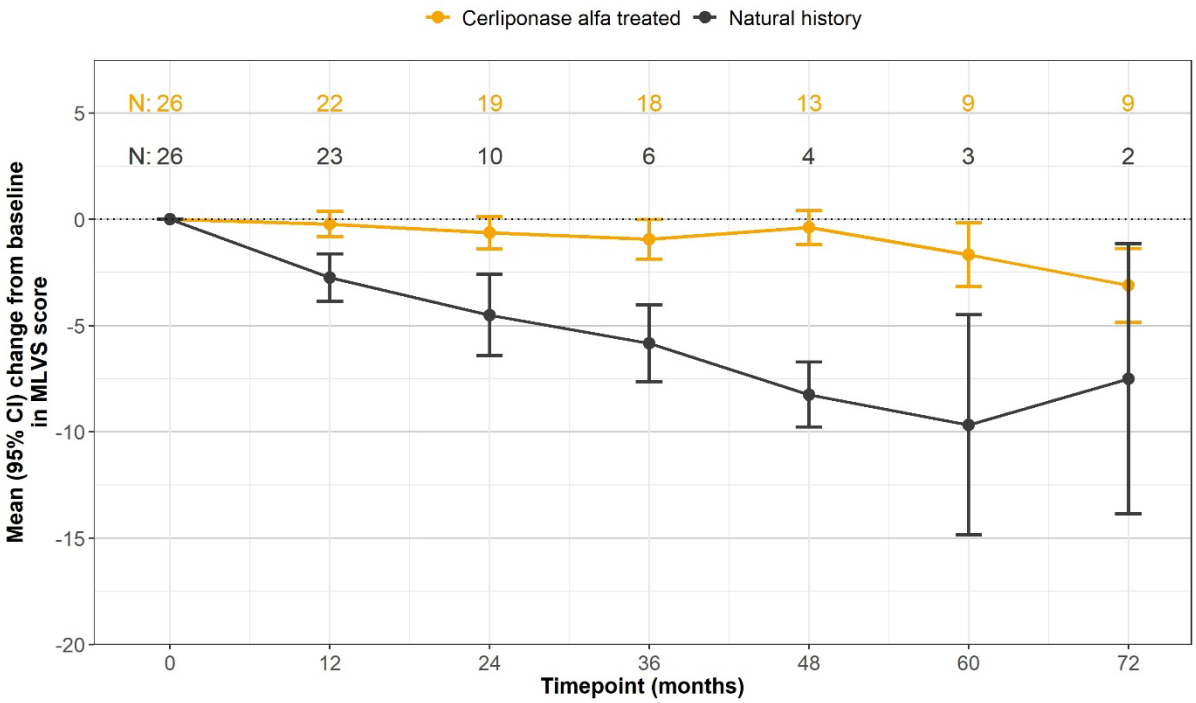
For ERG, OCT, VEP, Bayley Scales of Infant and Toddler Development (3rd Ed), Wechsler Preschool & Primary Scale of Intelligence (4th Ed), Vineland Adaptive Behaviour Scales outcomes, no formal quantitative analysis was conducted since only descriptive summary data were collected. The individual assessment notes for OCT, VEP, ERG are presented in the supplementary file “BioMarin-DataOnFile-Cerliponase alfa MAA _Database _SourceCut _Nov1.xlsx” (included in the reference pack). A summary of the assessments conducted are included in the response to clarification question A14, although there was no expectation of the CLN2 disease symptom of vision loss to be impacted by treatment with cerliponase alfa (see response to A14 for additional details).

The information collected and the level of analysis possible will become apparent upon review of the “BioMarin-DataOnFile-Cerliponase alfa MAA _Database _SourceCut _Nov1.xlsx” file. An uncorrupted version of this file is provided in the reference pack.

**CLN2 Clinical Rating Scale – MLVS score**

Using the same time windows as in Table 1, the change from baseline in CLN2-MLVS score at each year of follow-up is shown in Figure 33.

**Figure 33: Change from baseline in CLN2-MLVS score by year of follow-up (1:1 matched NH and MAA FAS)**

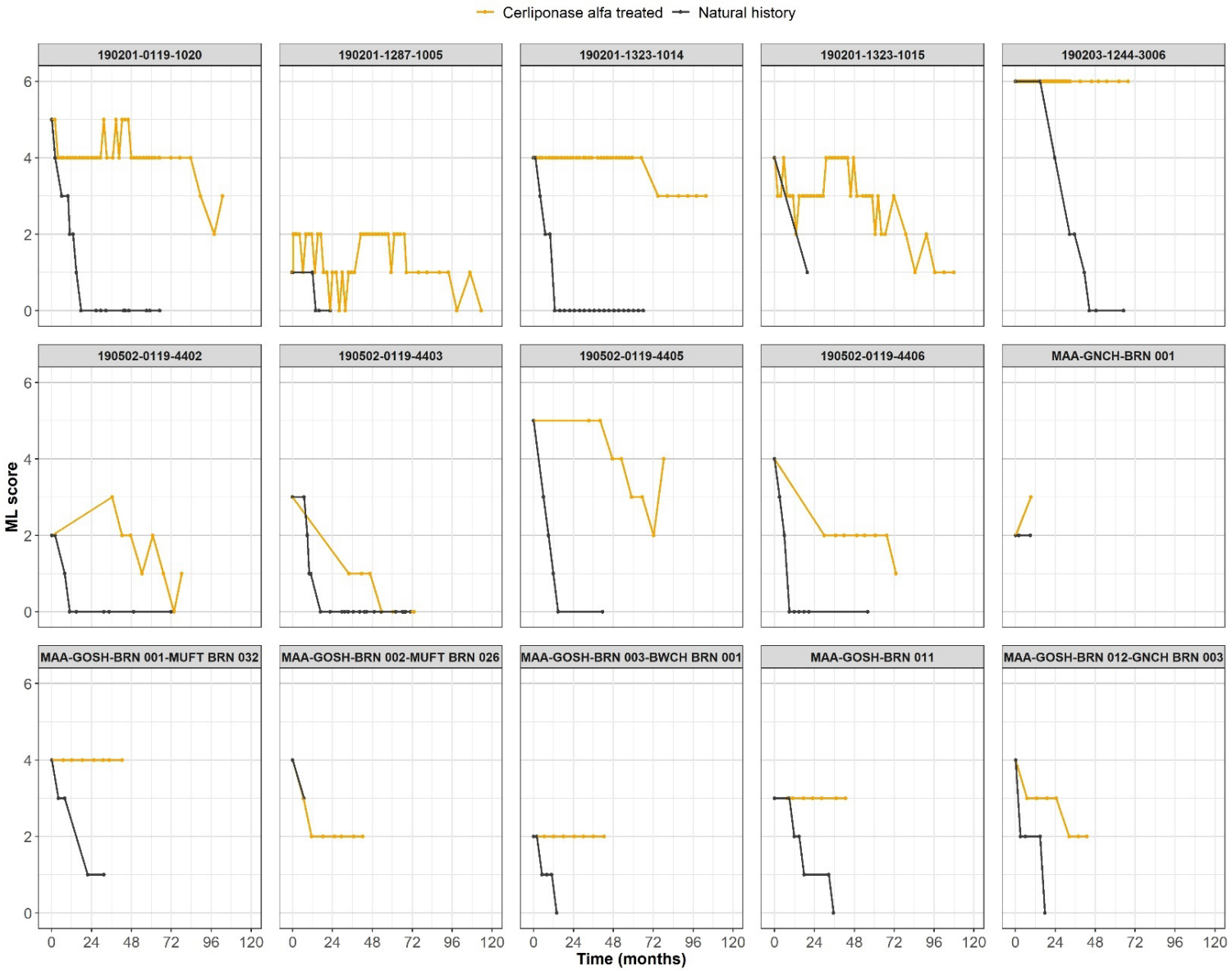



Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; MAA, managed access agreement; MLVS, motor language vision seizure; NH, natural history.

## A12. Priority question: The EAG would appreciate more individual-level information on patients in the MAA. Could you please provide or produce figures of ML score progression in the MAA for each patient, similar to those in Figure 11.4.1.1.5.1 of the CSR of trial 190-202 [BioMarin-DataOnFile-190 202 Final CSR 2021.pdf]

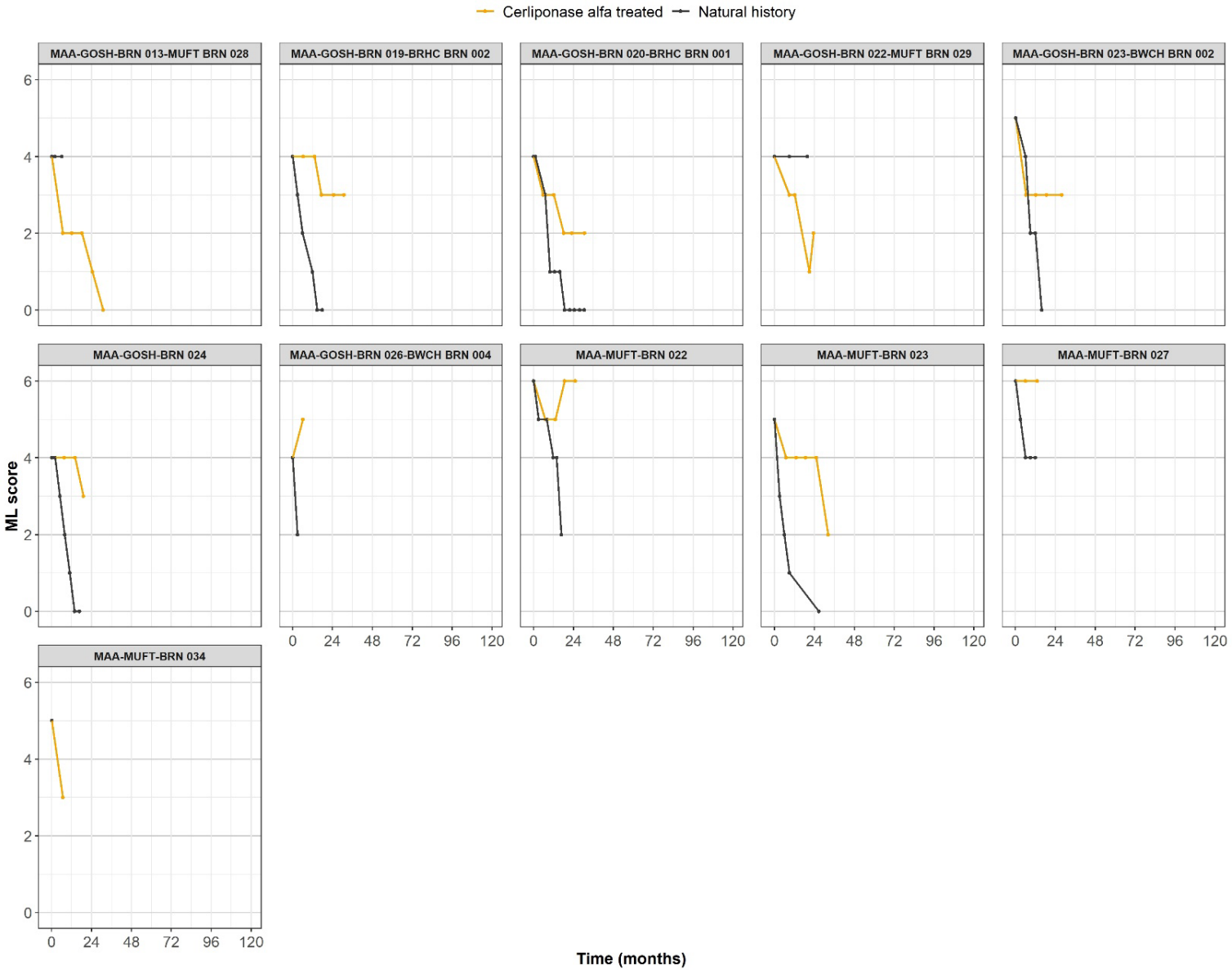
The CLN2-ML scores by subject over time for the 1:1 matched MAA FAS and natural history dataset are shown in Figure 34 and Figure 35.

**Figure 34: CLN2-ML scores by subject over time (1:1 matched NH and MAA FAS) (1)**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; MAA, managed access agreement; ML, motor language; NH, natural history.

**Figure 35: CLN2-ML scores by subject over time (1:1 matched NH and MAA FAS) (2)**




Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; MAA, managed access agreement; ML, motor language; NH, natural history.

**A13. The MAA data file supplied [BioMarin-DataOnFile-Cerliponase alfa MAA _Database _SourceCut _Nov1.xlsx] was corrupted and could not be opened. Please resend this file, preferably in a simple file format (such as CSV) to ensure it is readable.**

A new version of the MAA data file has been provided in the accompanying reference pack.

## *Vision and seizures*

**A14. Priority question: Please provide tables and/or figures of all vision loss data across trials 190-201/202, 190-203 and MAA (and other trials, where data exists) to verify the claim in CS section B.2.12.3 that "There was no significant indication that cerliponase alfa treatment could improve or stabilise vision loss". Please include data on both OCT and VA assessments.**

An overview of the collected visual outcomes collected across the 190-202 and 190-203 trials and the MAA data collection agreement is presented in Table 23.

**Table 23: Visual outcomes assessed across the relevant clinical effectiveness evidence**

| Visual outcome assessed | 190-201/2 | 190-203 | MAA |
|---|---|---|---|
| Clinical rating scale – Vision score | Yes | Yes | Yes |
| OCT | Yes | Yes | Yes – qualitative assessment only |
| Visual Acuity | Yes | Yes | Yes – qualitative assessment only |
| ERG | No | No | Yes – qualitative assessment only |

Abbreviations: ERG, electroretinogram; OCT, optical coherence tomography; MAA, managed access agreement; MLV, motor language vision.

Progressive vision loss in CLN2 patients has been shown to be due to both retinal changes and central changes in the brain (20, 21). The European Public Assessment Report (EPAR) summary of cerliponase alfa's pharmacokinetic profile states that the blood-retina barrier prevents cerliponase alfa from reaching therapeutic concentrations in the affected retinal cells when administered via ICV infusion (22). This is supported by animal studies of TPP1 enzyme replacement therapy (23, 24). As noted in the EAG report for HST12, whilst cerliponase alfa's distribution to the optical centres of the brain may influence the rate of progression of vision impairment, the treatment is not expected to have a significant effect upon vision loss in CLN2 disease (25).

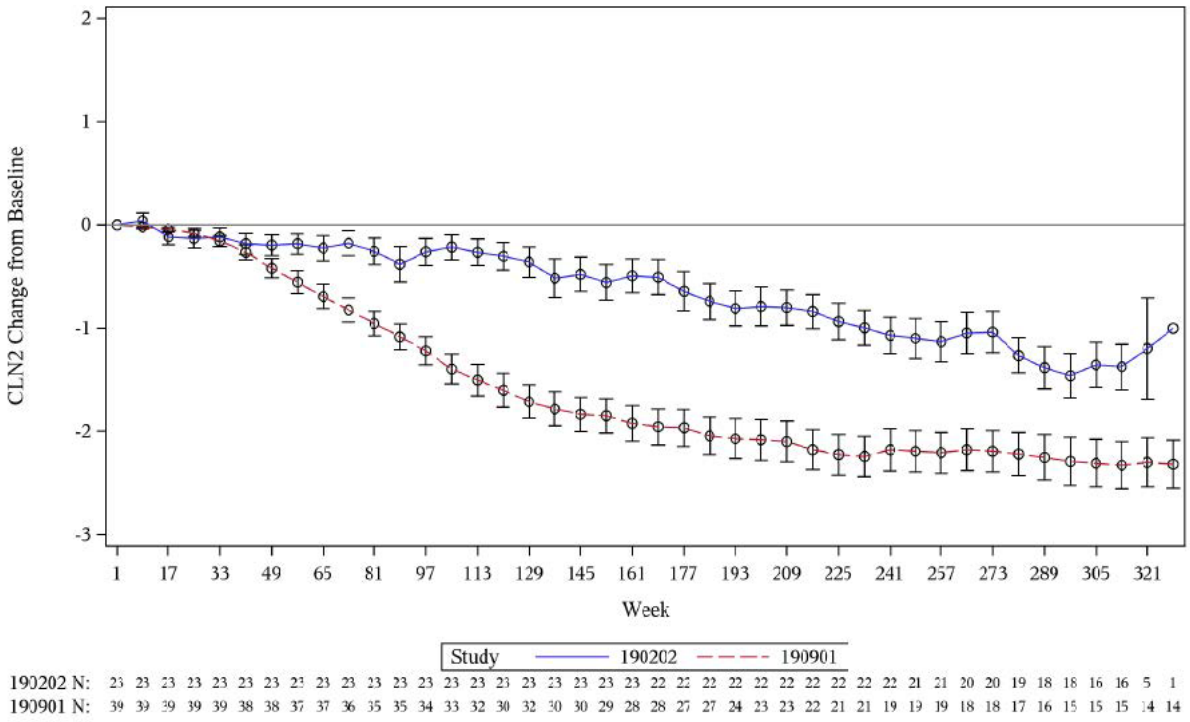
### CLN2 Clinical Rating Scale – Vision (V) domain

Figure 36 presents mean (± SE) change from baseline in the CLN2 Clinical Rating scale vision domain (0–3 point) for the ITT population vs natural history participants for 190-

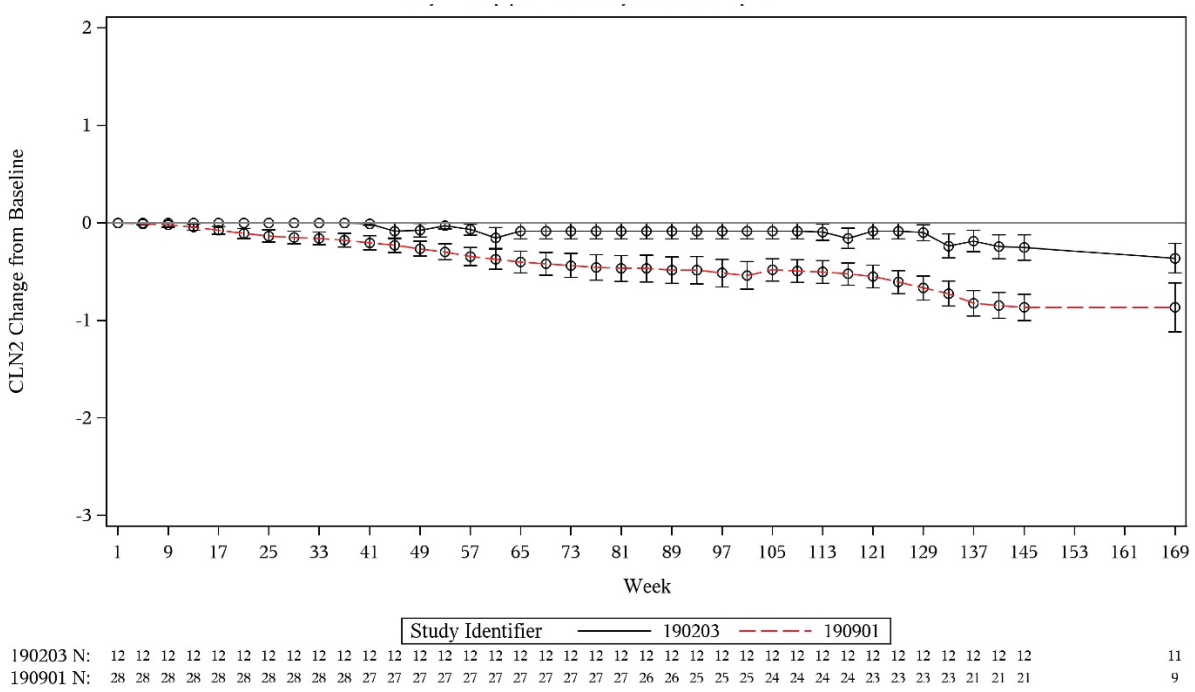
201/202, 190-203. **Error! Reference source not found.** presents the vision domain for the MAA full analysis set (FAS) cohort . There is a trend for a delay in decline of vision scores from baseline to last assessment across all three studies, compared with NH participants. The steeper decline in vision scores observed in Study 190-202 vs 190-203 participants, is likely due to the higher median age at baseline for participants in 190-202. Mean (SD) age at baseline was 5.0 (1.29) years vs 3.1 (1.45) years in 190-202 vs 190-203 participants, respectively. Whilst this evidence suggests cerliponase alfa treatment for CLN2 disease may slightly delay vision loss, there is no significant evidence to suggest vision loss is improved or stabilised.

**Figure 36: Change from baseline of CLN2-V domain score over time**

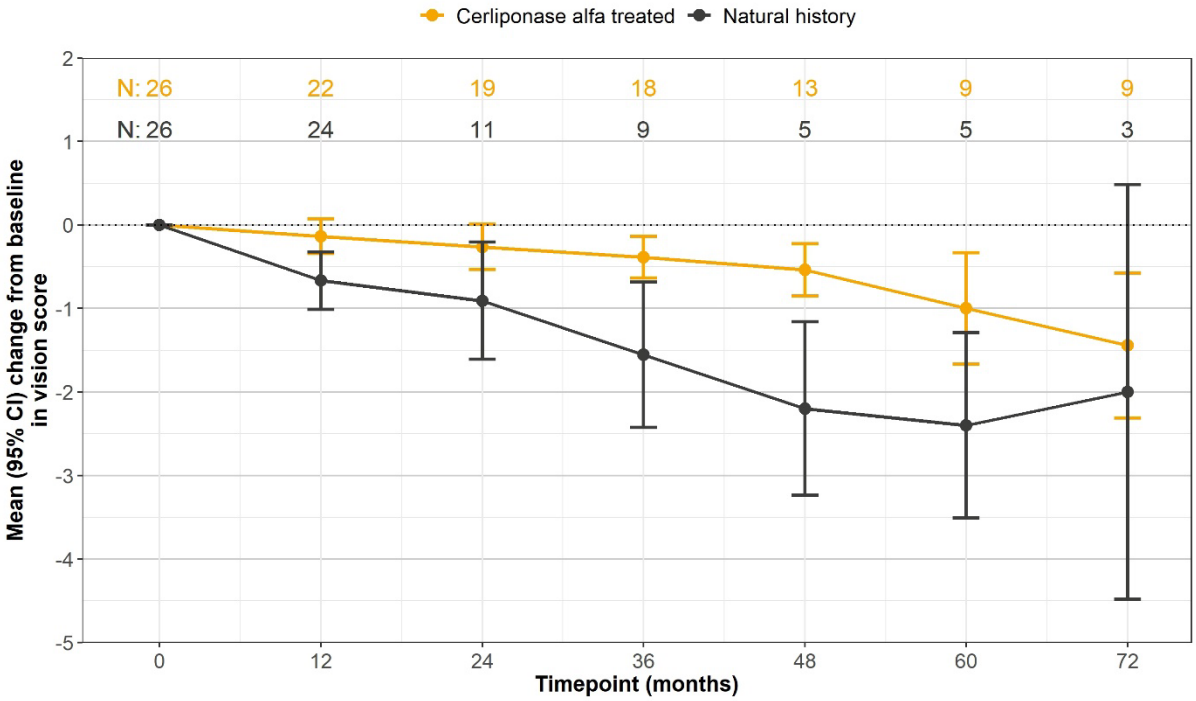
**A**




**B**



**C**




Sources: Study 190-202 CSR, 2021 (9); Study 190-203 CSR, 2023 (1); MAA database 2023 (10).
A. Evaluable 190-202 population vs 190-901 natural history evaluable population – mean score ±SE
B. Evaluable 190-203 population vs 190-901 natural history evaluable population – mean score ±SE
C. MAA FAS 1:1 matched to 190-901 natural history – mean score ± 95% CI
Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; MAA, managed access agreement; SE, standard error; V, vision.

### Optical coherence tomography (OCT)

Individual response data listings are included for OCT outcomes in the reference pack, as outlined in A2.

Note that no OCT measurements were conducted as part of Study 190-201 and there is limited OCT assessment data for Study 190-202, as the outcome was added as part of protocol amendment 6 (dated 17 December 2018). The MAA did not formally collect OCT assessment data and qualitative assessments are recorded in the [BioMarin-DataOnFile-Cerliponase alfa MAA _Database _SourceCut _Nov1.xlsx] file.

A summary of the OCT assessment outcomes across the relevant effectiveness studies is presented in Table 24.

**Table 24: OCT assessment summary**

| No of OCT assessments | Number of participants, n (%) | Time of assessment, n | Overview of outcome |
|---|---|---|---|
| **Study 190-202** | | | |
| 0 | 5 (22%) | NA | NA |
| 1 | 13 (57%) | Week 217: 4<br><br>Study Completion: 9 | One assessment was not evaluable, while the remainder were abnormal.<br>8 participants had reports of bilateral atrophy (macular atrophy [3 participants], foveal atrophy [2 participants], bull's eye atrophy, atrophy), while 4 had other reported abnormalities (unspecified abnormalities for both eyes [2 participants], bilateral mild foveal irregularities at sub RPE level [1 participant], and globally thin retina in both eyes [1 participant]) |
| 2 | 3 (13%) | Week 217: 3<br><br>Study Completion: 3 | 2 participants had bilateral reduction in retinal thickness at both assessments, while 1 had bilateral macular atrophy at both assessments |
| 3 | 2 (9%) | Week 193: 2<br>Week 217: 2<br>Study Completion: 2 | Both participants' tests reported marked retinopathy (describing a Weill Cornell ophthalmologic severity score of 5) in both eyes at all timepoints. Note both participants were >10 years old at last assessment |
| **Study 190-203** | | | |
| 1 | 14 (100%) | | 12/14 had their first OCT observation as abnormal. Of the 2/14 that has a normal first OCT observation one participant remained normal through last assessment, and one participant became abnormal by last assessment.<br>3/12 participants had a normal overall assessment at their last observation<br>9/12 participants had an abnormal overall assessment at their last observation |
| **MAA** | | | |
| No OCT data | 5 | NA | NE |
| Testing stopped/not clinically indicated | 7 | NA | NE |
| NE | 6 | NA | NE |
| 1 | 3 | NA | NE |
| 2 | 6 | NA | NE |
| 3 | 4 | NA | NE |
| 4 | 2 | NA | NE |

Abbreviations: NA, not applicable; NE, not evaluable; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

### Visual acuity assessment (VA)

No VA measurements were conducted as part of Study 190-201, and there is limited VA assessment data for Study 190-202 and Study 190-203, as the outcome was added as part of protocol amendments 6 (dated 17 December 2018) and 5 (dated 18 December 2018), respectively. The MAA did not formally collect VA assessment data and qualitative visual evoked potential assessments are recorded in the [BioMarin-DataOnFile-Cerliponase alfa MAA _Database _SourceCut _Nov1.xlsx] file.

A summary of the VA assessment outcomes across the relevant effectiveness studies is presented in Table 25.

**Table 25: VA assessment summary**

| No of VA assessments | Number of participants, n (%) | Time of assessment, n | Overview of outcome |
|---|---|---|---|
| **Study 190-202** | | | |
| 0 | 14 (61%) | NA | 3 participants had VA in the moderate visual impairment range (1 with 20/130 and 2 with 20/160), 3 participants had vision in the severe visual impairment range (20/250, 20/270, and 20/380), and 1 participant had profound visual impairment (1900).<br>Two participants had assessments where the VA could not be quantified. One participant was reported as “no response to largest card, intermittently following light.” An additional participant had “no interest in the teller cards, reasonably good visual behaviour, can fix and follow, makes good eye contact.” |
| 1 | 7 (30%) | Between Week 205 and the end of the study visit | |
| 2 | 1 (4%) | | |
| 3 | 1 (4%) | | |
| **Study 190-203** | | | |
| 0 | 4 | NA | NA |
| 2 | 5 | NR | Two participants had mild visual impairment (20/31, 20/47), 3 participants had moderate visual impairment (20/63, 20/100, 20/170), 4 participants had severe visual impairment range (20/250, 20/260, and 2 participants with 20/310), and 1 participant had profound visual impairment (20/1200). |
| 3 | 1 | | |
| 4 | 3 | | |
| 9 | 1 | | |
| **MAA** | | | |
| No VA data | 7 | NA | NE |

| No of VA assessments | Number of participants, n (%) | Time of assessment, n | Overview of outcome |
|---|---|---|---|
| Testing stopped/not clinically indicated | 5 | | NE |
| 1 | 8 | NA | NE |
| 2 | 3 | NA | NE |
| 3 | 6 | NA | NE |
| 4 | 4 | NA | NE |

For those subjects with more than one assessment, their worst binocular assessment is reported.
Abbreviations: MAA, managed access agreement; NA, not applicable; NE, not evaluable; NR, not reported; VA, visual acuity.

### A15. Clinical advice to the EAG suggested that cerliponase alpha may be beneficial in reducing frequency or severity of seizures. Please therefore provide a detailed summary of all seizure outcomes measured and data recorded for all trials, particularly with regard to:

1. **Frequency of seizures**
2. **Type and severity of seizures**
3. **Need for medication to control seizures**
4. **Seizures requiring hospital visits**

**Table 26: Overview of seizure outcomes across the relevant clinical effectiveness evidence**

| | 190-202 | 190-203 | MAA | 190-501 | 190-502 | 190-504 | 190-801 |
|---|---|---|---|---|---|---|---|
| Seizure information included in company submission | EEG: Document B, Section 2.6.5.2<br><br>Convulsion AE: Appendix F | EEG: Document B, Section 2.6.5.2<br><br>mUBDRS seizure inventory: Document B, Section 2.6.5.2<br><br>Convulsion AE: Appendix F | EEG: Document B, Section 2.6.5.2 | Convulsion AE: Appendix F | Convulsion AE: Appendix F | Convulsion AE: Appendix F | Appendix Q: All reported seizure data reported |
| **Additional seizure data presented** | | | | | | | |
| Type, frequency, and severity | CLN2 seizure (S) domain<br>Seizure AE incidence summary | CLN2 seizure (S) domain<br>Seizure AE incidence summary | CLN2 seizure (S) domain<br>Seizure AE incidence summary | Seizure AE incidence summary | Seizure AE incidence summary | Seizure AE incidence summary | NA |
| Need for medication | Yes | Yes | NR | Yes | NR | Yes | Yes |
| Seizures requiring hospital visits | NR | NR | NR | NR | NR | NR | Yes |

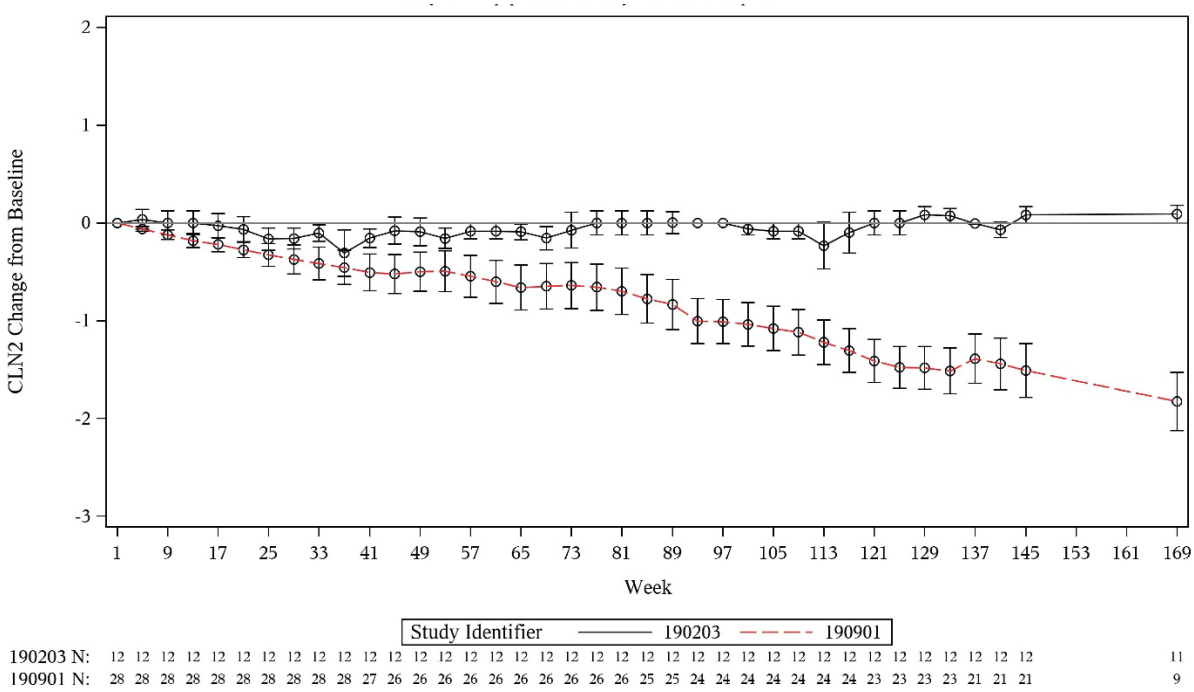
†DEM-CHILD-RX did not report any seizure data
Abbreviations: AE, adverse event; CLN2, neuronal ceroid lipofuscinosis 2; mUBDRS, Modified Unified Batten Disease Rating Scale; NA, not applicable.

**CLN2 Clinical Rating Scale – Seizure(S) domain**

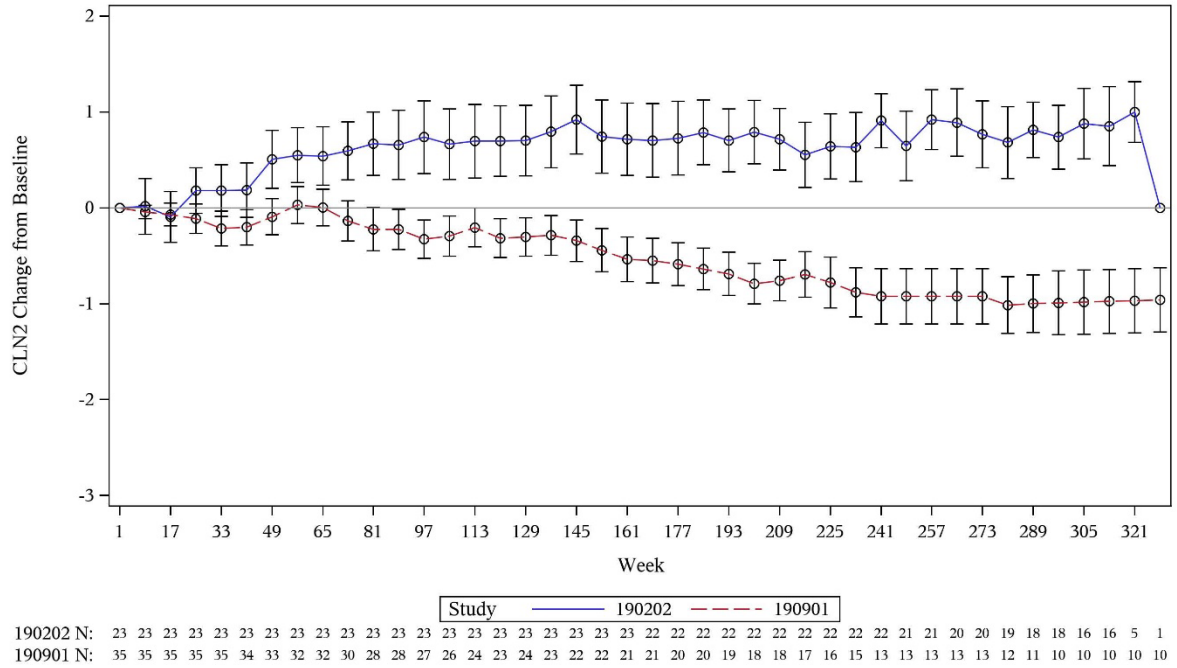
The seizure domain score of the CLN2 Clinical Rating scale provides an assessment of the frequency of generalised tonic-clonic seizures, the most commonly reported seizure for patients with CLN2. Mean (± SE) change from baseline in the CLN2 Clinical Rating scale seizure domain (0–3 point) is displayed for the ITT population vs natural history participants for 190-201/202 and 190-203, and the mean change (±95% CI) is displayed for MAA FAS vs 1:1 matched natural history participants (Figure 37). Cerliponase alfa treated participants exhibited a trend for stable, if not slightly improved, seizure scores across the evaluation period of all three studies, when compared with natural history participants.

**Figure 37: Change from baseline of CLN2-S domain score over time**

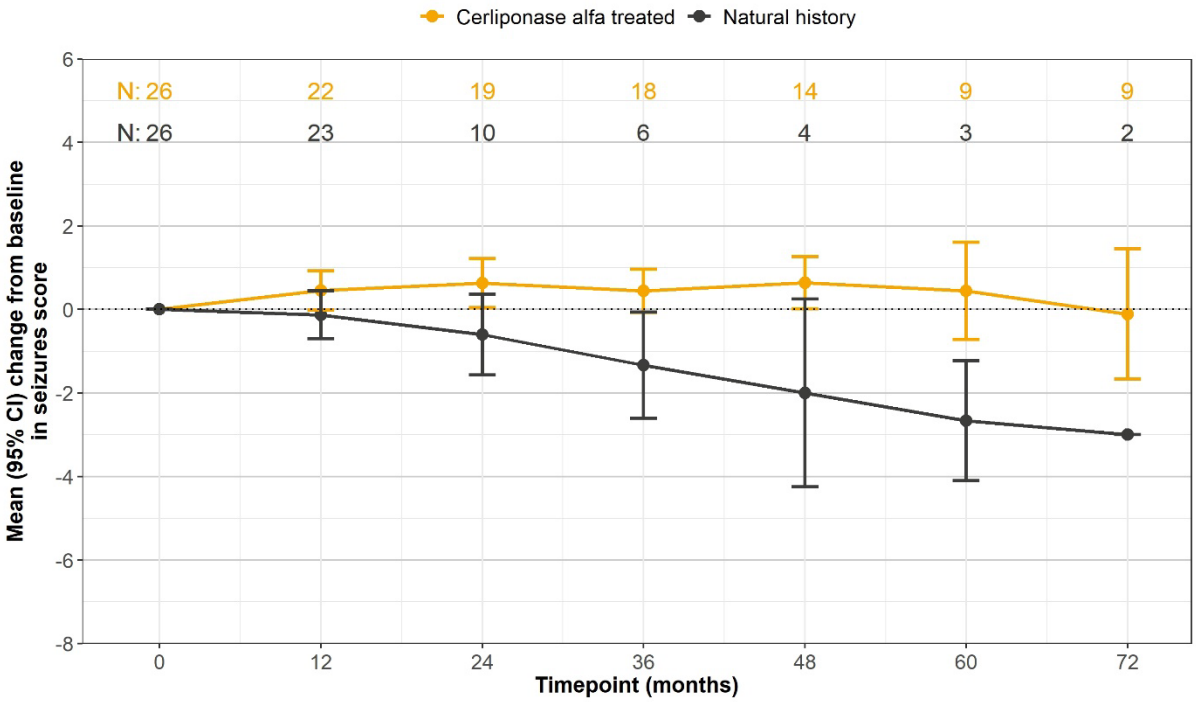
**A**



**B**




**C**




Sources: Study 190-202 CSR, 2021 (9); Study 190-203 CSR, 2023 (1); MAA database 2023 (10).
A. Evaluable Study 190-202 population vs 190-901 natural history evaluable population – mean score ± SE
B. Evaluable Study 190-203 population vs 190-901 natural history evaluable population – mean score ± SE
C. MAA FAS 1:1 matched to 190-901 natural history – mean score ± 95% CI
Abbreviations: CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2; MAA, managed access agreement; S, seizure; SE, standard error.

**Summary of seizure adverse events**

Table 27 presents a summary of the seizure adverse events and incidence reported. As there is no natural history comparator data, an assessment of changes to seizures over the cerliponase alfa evaluation period is not possible.

**Table 27: Summary of reported seizure adverse event incidence**

| | Study (reference) | | | | |
|---|---|---|---|---|---|
| Seizure type | 190-202 (9) | 190-203 (1) | 190-501 (15) | 190-502 (16) | 190-504 (17) |
| Convulsions | Convulsion AEs: Appendix F | Convulsion AEs: Appendix F | 7 (18%) experienced by 7 participants. Two of the events were assessed as Grade 2, 4 events as Grade 3, and 1 event as Grade 4. | – | 14 events reported in 7 participants: 4 events of seizure (in 2 participants) were assessed as related to cerliponase alfa |
| Generalised tonic-clonic | 250 AEs of generalised tonic clonic seizure in 16 subjects (67%) | 18 AEs in 6 participants (43%) | 1 (0.02%); SAE reported as related to cerliponase alfa | 6 (22%) | 1 (2%); SAE |
| Partial seizures | 15 AEs in 7 participants (29%) | 28 AEs in 3 participants (21%) | NR | 4 (15%) | NR |
| Tonic convulsion | 1 Grade 2 AE | NR | NR | 1 (4%) | NR |
| Atonic seizures | 6 AEs in 3 participants (13%) | NR | NR | 3 (11%) | NR |
| Petit mal epilepsy | 22 AEs in 8 participants (33%) | 1 (7.1%) | NR | 4 (15%) | NR |
| Epilepsy | 180 AEs in 13 participants (54%) | – | NR | 1 (4%) | 2 AEs in 2 participants (4.2%), 1 Grade 2 event and 1 Grade 3 |
| Status epilepticus | 2 AEs in 2 participants (8%) – Grade 3 and Grade 4 | 1 (7.1%) Grade 3 AE | 1 (0.02%); Grade 4 recurrent. Participant later passed away (see Document B, Section 2.10.1) | NR | 2 Grade 3 AEs in 2 participants (4.2%) |

| | Study (reference) | | | | |
|---|---|---|---|---|---|
| Other | – | – | – | – | 1 event of change in seizure presentation in 1 participant |

Abbreviations: AE, adverse event; NR, not reported; SAE, serious adverse event.

### Need for seizure medication

A summary of the evidence for seizures in cerliponase alfa treated participants that required medication, is presented in Table 28.

**Table 28: Need for seizure medication reported across the clinical effectiveness evidence**

| **Study 190-201/202** |
|---|
| BioMarin-DataonFile-190-202 Final CSR 2021 Figure 14.2.5.1 presents Study 190-201/202 plots of anti-epileptic treatment vs analysis day from start and end day, by subject for the ITT analysis population over the evaluation period (300 mg dosing period).<br>Most (21/23) participants were on anti-epileptics before initiating cerliponase alfa. In CLN2 disease, seizures are commonly refractory and require multiple medications. In this graphical representation, no clear pattern can be established. No temporal relationship was found between start and stop of anti-epileptic therapy, change in S score, and occurrence of convulsion AEs. |
| **Study 190-203** |
| Individual participant plots of anti-epileptic treatment by analysis day from start and end day, with indication whether prophylactic or acute use, were displayed with incidence of convulsion AEs per SMQ, 0–3 point S score (CLN2 clinical rating scale), and mUBDRS seizure score by analysis day for each participant in the ITT population.<br>Less than half (6/14) participants were on antiepileptics before initiating BMN 190. In CLN2 disease, seizures are commonly refractory and require multiple medications. Four participants without any medical history of seizure or development of seizures during the trial had sustained seizure domain scores of 3 points, sustained maximum mUBDRS seizure scores, and no anti-epileptic drug use for the duration of treatment. These four participants were all ≤2 years at baseline and completed their end of study visit (Week 145) between 3.8 to 4.7 years of age.<br>BioMarin-DataonFile-Study190-203 Final CSR Figure 14.2.11.1 presents Study 190-203 plots of anti-epileptic treatment vs analysis day from start and end day, by subject ITT population. |
| **MAA** |
| The need for medication to control seizures was an outcome not collected as part of the MAA. |
| **Study 190-501** |
| BioMarin-DataOnFile-190-501 interim-report-2023, Table 14.1.4.2 presents the concomitant medications, including medication for seizure control/epilepsy, taken on or after the initial dose of cerliponase alfa for Study 190-501 participants. |
| **Study 190-502** |
| Despite concomitant medication information collected as part of Study 190-502, this was not a reported outcome. |

| |
|---|
| **Study 190-504** |
| BioMarin-DataOnFile-Study 190-504 EMA Annual Report 2023 Table 14.1.4.2 presents the concomitant medication for seizure control/epilepsy taken on or after the initial dose of cerliponase alfa for Study 190-504 participants. |
| **Study 190-801** |
| Participant anti-epileptic medication change over the Study 190-801 evaluation period was presented in Appendix Q, Figure 2. |
| **DEMCHILD-RX** |
| The need for medication to control seizures was not collected during DEMCHILD-RX |

Abbreviations: AEs, adverse events; CLN2, neuronal ceroid lipofuscinosis 2; CSR, clinical study report; EMA, European Medicines Agency; ITT, intention-to-treat; MAA, managed access agreement; mUBDRS, Modified Unified Batten Disease Rating Scale; NA, not applicable; SMQs, Standardised MedDRA Queries.

**Seizures requiring hospital visits**

Seizures requiring hospitals were only recorded during Study 190-801. Appendix Q, Figure 3 presents the percentage of seizures in Study 190-801 participants that required doctor/hospital visits (19).

Although information was not formally collected, during the July 2023 advisory board with healthcare professionals experienced in treating patients with CLN2, advisors emphasised that seizures had been easier to manage in cerliponase alfa treated patients with CLN2 since the 2017 positive recommendation and the routine availability of cerliponase alfa treatment (7). Seizures were reported as less frequent, and less severe in patients receiving cerliponase alfa. Advisers also noted that in the past, a patient with CLN2 may have required hospitalisation for seizures, however this was less likely on cerliponase alfa treatment. During an advisory board with patient advocates, seizure severity was described as having a large impact on the QoL of patients and their families (6).

# Section B: Clarification on cost-effectiveness data

**Please note:** This clarification requests a number of scenario analyses to be conducted by the company. An updated model with functionality to conduct these analyses should be submitted alongside the company's response to points for clarification.

## *Transition probabilities*

### B1. Priority question: Transition probabilities for health states 1 to 7 are informed in the company's base-case by study 190-203.

1. **Please justify the company's preference for using this evidence source in the base-case given the greater sample size (and for some patients longer follow-up) in the 'all patient' pooled data.**

Data from Study 190-203 were used to inform transition probabilities in the base case because these transitions best align with the baseline characteristics used in the base case (i.e. patients from Study 190-203 who initiated treatment at age less than 3 years). Note that there are insufficient data to inform transitions based only on patients from Study 190-203 who initiated treatment at age less than 3 years.

Of the available data, patients from Study 190-203 who initiated treatment aged less than 3 years were considered to most closely reflect the population of patients who would receive cerliponase alfa in the near future (i.e. due to the expected improvements in both time to diagnosis, and time to initiation of treatment following diagnosis).

Although the pooled analysis provides a greater sample size, it is also associated with the following limitations:

- For some patients, cerliponase alfa was not a treatment option at the time of diagnosis, resulting in delayed initiation of treatment.
- Some patients experienced progression between the end of the expanded access program and the start of the MAA (i.e. in the period in which they were not receiving treatment with cerliponase alfa).
- The COVID-19 pandemic is expected to have delayed both diagnosis and treatment in some patients, and also impacted on access to ancillary therapies.

- These data do not account for earlier diagnosis and treatment of patients due to availability of cerliponase alfa and increasing awareness of CLN2 disease.

**2. Please provide for the 'all patient' pooled data (matched to Study 190-901):**

**a. Clarification on why available data from Study 190-801 was not included on the pooled dataset;**

Study 190-801 was not included in the pooled dataset as this study did not include ML score analysis over time as a primary outcome. The Wave 1 analysis was focused on assessing changes in frequency and severity of seizures and seizure complications, as well as onset, frequency and severity of movement disorders in cerliponase alfa treated participants.

**b. Details on how data from patients who switched from the cerliponase the clinical trial programme to the MAA were handled (e.g., was evidence from the full follow-up across studies considered?);**

In the matched 'all patients' cerliponase alfa dataset there were five patients who transitioned from the clinical trial programme to the MAA. Of the five patients who transitioned to the MAA, two patients were from 190-202 and three patients were from 190-502. These patients had their baseline and subsequent assessments taken from their respective clinical trial until the end of trial follow-up; the final assessments were then taken from the MAA.

**c. For each study in the pooled data (including MAA) the number of patients included, and the total number of patients in the 'all patients' dataset.**

Table 29 presents the number of patients included from each study in the cerliponase alfa 'all patients' matched dataset and the natural history matched dataset. In total, there were 40 matched cerliponase alfa patients and 40 matched natural history patients.

**Table 29: The number of patients from each study in the cerliponase alfa 'all patients' matched dataset and the natural history matched dataset**

| Study | Number of patients |
|---|---|
| **Cerliponase alfa 'all patients' matched dataset** | 40 |
| MAA "new starter" | 11 |
| MAA "ex-trial" from 190-202 | 2 |
| MAA "ex-trial" from 190-502 | 3 |

| Study | Number of patients |
|---|---|
| 190-202 | 13 |
| 190-203 | 11 |
| **Natural history matched dataset** | 40 |

Abbreviations: MAA, managed access agreement.

### d. Baseline characteristics (same variables as in Table 13 of the CS) by treatment group.

Detailed baseline characteristics for the cerliponase alfa 'all patients' matched dataset and the natural history matched dataset are presented in Table 30.

**Table 30: Baseline characteristics for NH and cerliponase alfa 'all patients' (1:1 matched patients)**

| | NH (N=40) | Cerliponase alfa 'all patients' (N=40) |
|---|---|---|
| Age at baseline, years | | |
| Mean (SD) | 4.13 (1.28) | 4.16 (1.26) |
| Median (min, max) | 4.21 (1.08, 8.75) | 4.17 (1.07, 8.5) |
| Sex, n (%) | | |
| Female | 18 (45.0%) | 18 (45.0%) |
| Male | 22 (55.0%) | 11 (27.5%) |
| Unknown | 0 (0.0%) | 11 (27.5%) |
| Genome n (%) | NR | NR |
| CLN2 motor score | | |
| Mean (SD) | 2.10 (0.71) | 2.00 (0.72) |
| Median (min, max) | 2 (1, 3) | 2 (1, 3) |
| CLN2 language score | | |
| Mean (SD) | 1.78 (0.83) | 1.88 (0.82) |
| Median (min, max) | 2 (0, 3) | 2 (0, 3) |
| CLN2 ML score | | |
| Mean (SD) | 3.88 (1.42) | 3.88 (1.42) |
| Median (min, max) | 4 (1, 6) | 4 (1, 6) |
| CLN2 MLVS score | | |
| n | 39 | 40 |
| Mean (SD) | 8.33 (2.49) | 8.88 (2.10) |
| Median (min, max) | 8 (4, 12) | 9 (3, 12) |
| Age at disease onset, months† | | |
| n | 39 | 20 |
| Mean (SD) | 34.9 (8.52) | 33.5 (7.53) |
| Median (min, max) | 36 (15, 53) | 35.5 (18, 43) |
| Age of first seizure, months | | |
| n | 40 | 20 |
| Mean (SD) | 38.6 (13.9) | 38.2 (6.28) |
| Median (min, max) | 36 (21, 106) | 37.7 (30.0, 56.2) |

Source: BioMarin MAA database, 2023 (10).
†Defined as age at first symptom.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; FAS, full analysis set; L, language; MAA, managed

access agreement; M, motor language; ML, motor language; MLVS, motor language vision seizure; NH, natural history; NR, not reported; S, seizure; SD, standard deviation, V, vision.

## B2. Priority question: The detail provided by the company on the calculation of the transition probabilities for health states 1 to 7 is insufficient for the EAG to provide a critique. Please provide the following elements:

### a) Annotated R code used to estimate the transition probabilities with the MSM R package;

The file 'Example MSM transition code' contains the requested annotated R code and has been provided in the accompanying reference pack.

### b) Details on how the model was specified (including potential covariate selection), initial values used and information on whether any parameters were fixed at their initial values, with justifications for these selections and choices;

For the economic model there were five models estimated using the 'msm' package to inform the transition intensities:

- Cerliponase alfa "all patients" (1:1 matching)
- Cerliponase alfa 190-203 patients (1:1 matching)
- Cerliponase alfa "all patients" (1:1 matching) piecewise at 6 months
- Natural history patients (1:1 matching)
- Natural history patients who were matched to 190-203 patients (1:1 matching)

**Cerliponase alfa "all patients" (1:1 matching)**

The model was specified by the formula state ~ time, where state and time were vectors containing the observed states and the corresponding observation times in weeks. The states were intermittently observed in time. Given the small patient numbers in each transition no additional covariates were included because exploratory testing yielded estimates with very large standard errors. There were seven states:

- State 1 – ML 0
- State 2 – ML 1

- State 3 – ML 2
- State 4 – ML 3
- State 5 – ML 4
- State 6 – ML 5
- State 7 – ML 6

An additional input for the model was a vector of subject identification numbers for the data specified in the previous formula. The following 7x7 matrix was specified which indicates the allowed transitions in the continuous-time Markov chain, and the initial values of those transitions (Table 31). An arbitrary initial value of 0.01 was chosen. A zero entry in the transition matrix represents that the instantaneous transition is not allowed. Therefore, transitions were restricted to adjacent states. If a patient was observed in state 4 at one observation and state 2 at the next observation, it was assumed that the patient must have gone through state 3 in between visits.

**Table 31: Transition matrix for cerliponase alfa "all patients" (1:1 matching)**

| | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|
| **1** | 0 | 0.01 | 0 | 0 | 0 | 0 | 0 |
| **2** | 0.01 | 0 | 0.01 | 0 | 0 | 0 | 0 |
| **3** | 0 | 0.01 | 0 | 0.01 | 0 | 0 | 0 |
| **4** | 0 | 0 | 0.01 | 0 | 0.01 | 0 | 0 |
| **5** | 0 | 0 | 0 | 0.01 | 0 | 0.01 | 0 |
| **6** | 0 | 0 | 0 | 0 | 0.01 | 0 | 0.01 |
| **7** | 0 | 0 | 0 | 0 | 0 | 0.01 | 0 |

Note: Transition matrix represents the transitions from row state to column state.

**Cerliponase alfa 190-203 (1:1 matching)**

The cerliponase alfa 190-203 dataset was the subgroup of patients from the cerliponase alfa 'all patients' dataset that were enrolled in Study 190-203. The model was specified by the same formula state ~ time, with no additional covariates. The following 7x7 matrix was specified which indicates the allowed transitions in the continuous-time Markov chain, and the initial values of those transitions (Table 32). There were no observations from or to state 1 in the 190-203 patients, therefore the entries (1, 2) and (2, 1) were set to zero. The same, arbitrary, initial value of 0.01 was chosen.

**Table 32: Transition matrix for cerliponase alfa 190-203 (1:1 matching)**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| **1** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **2** | 0 | 0 | 0.01 | 0 | 0 | 0 | 0 |
| **3** | 0 | 0.01 | 0 | 0.01 | 0 | 0 | 0 |
| **4** | 0 | 0 | 0.01 | 0 | 0.01 | 0 | 0 |
| **5** | 0 | 0 | 0 | 0.01 | 0 | 0.01 | 0 |
| **6** | 0 | 0 | 0 | 0 | 0.01 | 0 | 0.01 |
| **7** | 0 | 0 | 0 | 0 | 0 | 0.01 | 0 |

Note: Transition matrix represents the transitions from row state to column state.

### Cerliponase alfa “all patients” (1:1 matching) piecewise at 6 months

The model was specified by the same formula state ~ time, with no additional covariates. The same seven states and transition matrix were used as in the cerliponase alfa ‘all patients’ model (Table 31). An arbitrary initial value of 0.01 was chosen. Additionally, the model was defined piecewise at 26 weeks (six months) such that the transition intensities change at this timepoint. Six months was chosen as the cut-off for the piecewise model because patients treated with cerliponase alfa are expected to reach full therapeutic benefit by this time point. Therefore, it was anticipated that cerliponase alfa patients will have different transition intensities before and after the six months cut off.

### Natural history patients (1:1 matching)

The model was specified by the same formula state ~ time, with no additional covariates. The following 7x7 matrix was specified which indicates the allowed transitions in the continuous-time Markov chain, and the initial values of those transitions (Table 32). Across the matched natural history patients there were no observations showing an increase in ML score. Therefore, entries in the transition matrix that showed an increase in state were now set to zero. The same arbitrary initial value of 0.01 was used.

**Table 33: Transition matrix for natural history patients (1:1 matching)**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0.01 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0.01 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0.01 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0.01 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0.01 | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 | 0 | 0.01 | 0 |

**Natural history patients who were matched to 190-203 patients (1:1 matching)**

The natural history patients who were matched to 190-203 patients were the subgroup of natural history patients who were matched to patients from the cerliponase alfa 'all patients' dataset that were enrolled in Study 190-203. The model was specified by the same formula state ~ time, with no additional covariates. The same seven states were used as in the cerliponase alfa 'all patients' model and the same transition matrix as the full natural history dataset was used (Table 30). The same arbitrary initial value of 0.01 was used.

## c) Provide the number of observations used to inform each transition;

**Cerliponase alfa "all patients" (1:1 matching)**

The number of observations per transition in the cerliponase alfa "all patients" (1:1 matching) is provided in Table 34.

**Table 34**: **The number of observations per transition for cerliponase alfa "all patients" (1:1 matching)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 8 | 4 | 0 | 1 | 0 | 0 | 0 |
| **State 2** | 6 | 98 | 11 | 1 | 2 | 0 | 0 |
| **State 3** | 0 | 22 | 236 | 11 | 1 | 0 | 0 |
| **State 4** | 1 | 2 | 25 | 153 | 14 | 0 | 0 |
| **State 5** | 0 | 0 | 3 | 25 | 138 | 3 | 0 |
| **State 6** | 0 | 0 | 0 | 2 | 6 | 24 | 3 |
| **State 7** | 0 | 0 | 0 | 0 | 0 | 4 | 210 |

Note: The table represents the transitions from row state to column state.

**Cerliponase alfa 190-203 patients (1:1 matching)**

The number of observations per transition in the cerliponase alfa 190-203 patients (1:1 matching) is provided in Table 35.

**Table 35**: **The number of observations per transition for cerliponase alfa 190-203 patients (1:1 matching)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **State 2** | 0 | 1 | 3 | 0 | 0 | 0 | 0 |
| **State 3** | 0 | 2 | 64 | 2 | 0 | 0 | 0 |
| **State 4** | 0 | 0 | 5 | 29 | 5 | 0 | 0 |
| **State 5** | 0 | 0 | 0 | 7 | 50 | 1 | 0 |
| **State 6** | 0 | 0 | 0 | 0 | 2 | 12 | 2 |
| **State 7** | 0 | 0 | 0 | 0 | 0 | 2 | 172 |

Note: The table represents the transitions from row state to column state

### Cerliponase alfa “all patients” (1:1 matching) piecewise at 6 months

The number of observations per transition in the cerliponase alfa “all patients” (1:1 matching) before 6 months and after 6 months is provided in Table 36 and Table 37, respectively.

**Table 36**: **The number of observations per transition for cerliponase alfa “all patients” (1:1 matching) before 6 months**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **State 2** | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **State 3** | 0 | 1 | 16 | 0 | 0 | 0 | 0 |
| **State 4** | 1 | 0 | 2 | 23 | 5 | 0 | 0 |
| **State 5** | 0 | 0 | 0 | 6 | 24 | 1 | 0 |
| **State 6** | 0 | 0 | 0 | 0 | 1 | 7 | 0 |
| **State 7** | 0 | 0 | 0 | 0 | 0 | 0 | 28 |

Note: The table represents the transitions from row state to column state.

**Table 37**: **The number of observations per transition for cerliponase alfa “all patients” (1:1 matching) after 6 months**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 8 | 3 | 0 | 0 | 0 | 0 | 0 |
| **State 2** | 6 | 97 | 9 | 1 | 1 | 0 | 0 |
| **State 3** | 0 | 21 | 214 | 9 | 1 | 0 | 0 |
| **State 4** | 0 | 1 | 23 | 123 | 9 | 0 | 0 |
| **State 5** | 0 | 0 | 1 | 15 | 110 | 2 | 0 |
| **State 6** | 0 | 0 | 0 | 0 | 5 | 16 | 2 |
| **State 7** | 0 | 0 | 0 | 0 | 0 | 3 | 174 |

Note: The table represents the transitions from row state to column state.

**Natural history patients (1:1 matching)**

The number of observations per transition in the natural history patients (1:1 matching) is provided in Table 38.

**Table 38:The number of observations per transition for the natural history patients (1:1 matching)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 100 | 0 | 0 | 0 | 0 | 0 | 0 |
| **State 2** | 21 | 9 | 0 | 0 | 0 | 0 | 0 |
| **State 3** | 6 | 15 | 14 | 0 | 0 | 0 | 0 |
| **State 4** | 0 | 7 | 13 | 9 | 0 | 0 | 0 |
| **State 5** | 0 | 1 | 6 | 7 | 11 | 0 | 0 |
| **State 6** | 0 | 0 | 0 | 5 | 5 | 6 | 0 |
| **State 7** | 0 | 0 | 0 | 0 | 1 | 7 | 12 |

Note: The table represents the transitions from row state to column state.

**Natural history patients who were matched to 190-203 patients (1:1 matching)**

The number of observations per transition in the natural history patients who were matched to 190-203 patients (1:1 matching) is provided in Table 39.

**Table 39:The number of observations per transition for the natural history patients who were matched to 190-203 patients (1:1 matching)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 21 | 0 | 0 | 0 | 0 | 0 | 0 |
| **State 2** | 7 | 3 | 0 | 0 | 0 | 0 | 0 |
| **State 3** | 3 | 5 | 4 | 0 | 0 | 0 | 0 |
| **State 4** | 0 | 1 | 5 | 3 | 0 | 0 | 0 |
| **State 5** | 0 | 0 | 2 | 3 | 2 | 0 | 0 |
| **State 6** | 0 | 0 | 0 | 2 | 2 | 5 | 0 |
| **State 7** | 0 | 0 | 0 | 0 | 1 | 4 | 11 |

Note: The table represents the transitions from row state to column state.

## d) Provide intensity matrices with standard errors and transition probability matrices with confidence intervals;

Note that the transition probabilities presented in response to this question differ slightly from those used in the electronic model; in the electronic model, weekly transition intensities (assuming a maximum transition of one state) are converted to 2-weekly transition probabilities (also assuming a maximum transition of one state). The transition probabilities

generated by the 'msm' package (presented below) allow for transitions of more than one state and are generated based on the instantaneous transition intensities rather than the discretised weekly rate.

### Cerliponase alfa "all patients" (1:1 matching)

Table 40 provide the transition intensity matrix with standard errors (SE) for the matched cerliponase alfa "all patients". Table 41 provides the transition probability matrix over a one week time interval for the matched cerliponase alfa "all patients".

**Table 40: Transition intensity matrix for cerliponase alfa "all patients" (1:1 matching); mean (SE)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | -0.031 (0.017) | 0.031 (0.017) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 2** | 0.008 (0.003) | -0.021 (0.005) | 0.014 (0.004) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 3** | 0 (0) | 0.011 (0.002) | -0.017 (0.003) | 0.007 (0.002) | 0 (0) | 0 (0) | 0 (0) |
| **State 4** | 0 (0) | 0 (0) | 0.019 (0.004) | -0.031 (0.005) | 0.012 (0.003) | 0 (0) | 0 (0) |
| **State 5** | 0 (0) | 0 (0) | 0 (0) | 0.030 (0.006) | -0.033 (0.006) | 0.003 (0.002) | 0 (0) |
| **State 6** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.035 (0.013) | -0.048 (0.015) | 0.013 (0.008) |
| **State 7** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.003 (0.002) | -0.003 (0.002) |

Note: The table represents the transitions from row state to column state.
Abbreviations: SE, standard error.

**Table 41: Transition probability matrix at one week for cerliponase alfa "all patients" (1:1 matching); mean (CI)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0.969 (0.929, 0.991) | 0.031 (0.009, 0.070) | 0.000 (0.000, 0.001) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0.007 (0.004, 0.019) | 0.979 (0.966, 0.986) | 0.013 (0.008, 0.022) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0 (0, 0) | 0.011 (0.007, 0.014) | 0.983 (0.976, 0.987) | 0.006 (0.004, 0.011) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0 (0, 0) | 0.019 (0.013, 0.028) | 0.969 (0.956, 0.976) | 0.012 (0.008, 0.020) | 0 (0, 0) | 0 (0, 0) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0.000 (0.000, 0.001) | 0.029 (0.021, 0.043) | 0.968 (0.952, 0.976) | 0.003 (0.001, 0.010) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.000 (0.000, 0.001) | 0.033 (0.017, 0.067) | 0.953 (0.909, 0.973) | 0.013 (0.005, 0.033) |
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.003 (0.001, 0.007) | 0.997 (0.993, 0.999) |

Note: The table represents the transitions from row state to column state.
Abbreviations: CI, confidence interval.

### Cerliponase alfa 190-203 patients (1:1 matching)

Table 40 provide the transition intensity matrix with SEs for the matched cerliponase alfa 190-203 patients. Table 43 provides the transition probability matrix over a one week time interval for the matched cerliponase alfa 203 patients.

**Table 42: Transition intensity matrix for cerliponase alfa 190-203 patients (1:1 matching); mean (SE)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 2** | 0 (0) | -0.224 (0.160) | 0.224 (0.160) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 3** | 0 (0) | 0.011 (0.008) | -0.016 (0.009) | 0.006 (0.004) | 0 (0) | 0 (0) | 0 (0) |
| **State 4** | 0 (0) | 0 (0) | 0.033 (0.015) | -0.070 (0.023) | 0.037 (0.017) | 0 (0) | 0 (0) |
| **State 5** | 0 (0) | 0 (0) | 0 (0) | 0.034 (0.013) | -0.039 (0.014) | 0.005 (0.005) | 0 (0) |
| **State 6** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.028 (0.020) | -0.058 (0.029) | 0.030 (0.021) |
| **State 7** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.002 (0.002) | -0.002 (0.002) |

Note: The table represents the transitions from row state to column state.
Abbreviations: SE, standard error.

**Table 43: Transition probability matrix at one week for cerliponase alfa 203 patients (1:1 matching); mean (CI)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 1.000 (1.000, 1.000) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0 (0, 0) | 0.800 (0.446, 0.959) | 0.199 (0.041, 0.552) | 0.001 (0.000, 0.004) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0 (0, 0) | 0.009 (0.002, 0.030) | 0.985 (0.958, 0.995) | 0.006 (0.002, 0.021) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0.000 (0.000, 0.001) | 0.032 (0.014, 0.073) | 0.933 (0.885, 0.958) | 0.035 (0.016, 0.078) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0.001 (0.000, 0.002) | 0.032 (0.015, 0.063) | 0.963 (0.928, 0.982) | 0.004 (0.000, 0.030) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.000 (0.000, 0.003) | 0.026 (0.006, 0.113) | 0.944 (0.837, 0.974) | 0.029 (0.007, 0.103) |
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.002 (0.001, 0.009) | 0.998 (0.991, 0.999) |

Note: The table represents the transitions from row state to column state.
Abbreviations: CI, confidence interval.

### Cerliponase alfa “all patients” (1:1 matching) piecewise at 6 months

Table 42 provide the transition intensity matrix with SEs for the matched cerliponase alfa “all patients” piecewise at 6 months. Table 45 provides the transition probability matrix over a one week time interval for the matched cerliponase alfa “all patients” piecewise at 6 months.

**Table 44: Transition intensity matrix for cerliponase alfa “all patients” piecewise at 6 months (1:1 matching); mean (SE)**

| | Baseline | | | | | | |
|---|---|---|---|---|---|---|---|
| **To<br>From** | **State 1** | **State 2** | **State 3** | **State 4** | **State 5** | **State 6** | **State 7** |
| **State 1** | -0.036 (0.022) | 0.036 (0.022) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 2** | 0.010 (0.005) | -0.028 (0.007) | 0.018 (0.005) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 3** | 0 (0) | 0.012 (0.003) | -0.017 (0.005) | 0.006 (0.004) | 0 (0) | 0 (0) | 0 (0) |
| **State 4** | 0 (0) | 0 (0) | 0.019 (0.004) | -0.030 (0.005) | 0.011 (0.003) | 0 (0) | 0 (0) |

| Baseline | | | | | | | |
|---|---|---|---|---|---|---|---|
| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
| **State 5** | 0 (0) | 0 (0) | 0 (0) | 0.027 (0.006) | -0.029 (0.006) | 0.003 (0.002) | 0 (0) |
| **State 6** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.032 (0.013) | -0.046 (0.015) | 0.014 (0.008) |
| **State 7** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.003 (0.002) | -0.003 (0.002) |
| **Time [26, Inf]** | | | | | | | |
| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
| **State 1** | 0 (0) | -3.109 (2.271) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 2** | -3.458 (2.091) | 0 (0) | -2.752 (1.049) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 3** | 0 (0) | -0.690 (0.908) | 0 (0) | 1.583 (5.398) | 0 (0) | 0 (0) | 0 (0) |
| **State 4** | 0 (0) | 0 (0) | 0.137 (0.570) | 0 (0) | -1.400 (0.578) | 0 (0) | 0 (0) |
| **State 5** | 0 (0) | 0 (0) | 0 (0) | -1.071 (0.444) | 0 (0) | -0.797 (1.242) | 0 (0) |
| **State 6** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | -0.433 (0.762) | 0 (0) | 1.139 (3.622) |
| **State 7** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | -0.258 (1.435) | 0 (0) |

Note: The table represents the transitions from row state to column state.
Abbreviations: Inf, infinity; SE, standard error.

**Table 45: Transition probability matrix at one week for cerliponase alfa "all patients" piecewise at 6 months (1:1 matching); mean (CI)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0.634 (0.043, 0.989) | 0.331 (0.009, 0.876) | 0.035 (0.000, 0.358) | 0.000 (0.000, 0.051) | 0.000 (0.000, 0.001) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0.126 (0.004, 0.465) | 0.719 (0.259, 0.932) | 0.155 (0.009, 0.563) | 0.000 (0.000, 0.121) | 0.000 (0.000, 0.003) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0.002 (0.000, 0.019) | 0.017 (0.001, 0.099) | 0.980 (0.006, 0.996) | 0.001 (0.000, 0.938) | 0.000 (0.000, 0.030) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0.000 (0.000, 0.001) | 0.016 (0.001, 0.032) | 0.949 (0.894, 0.976) | 0.035 (0.012, 0.092) | 0.000 (0.000, 0.001) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0.001 (0.000, 0.001) | 0.062 (0.029, 0.109) | 0.932 (0.879, 0.965) | 0.005 (0.000, 0.038) | 0.000 (0.000, 0.018) |

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.001 (0.000, 0.005) | 0.043 (0.005, 0.098) | 0.950 (0.000, 0.982) | 0.005 (0.000, 0.995) |
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.000 (0.000, 0.001) | 0.004 (0.000, 0.043) | 0.996 (0.956, 1.000) |

Note: The table represents the transitions from row state to column state.
Abbreviations: CI, confidence interval.

### Natural history patients (1:1 matching)

Table 46 provide the transition intensity matrix with SEs for the matched natural history patients. Table 47 provides the transition probability matrix at one week for the matched natural history patients.

**Table 46: Transition intensity matrix for natural history patients (1:1 matching); mean (SE)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 2** | 0.039 (0.008) | -0.039 (0.008) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 3** | 0 (0) | 0.048 (0.010) | -0.048 (0.010) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 4** | 0 (0) | 0 (0) | 0.059 (0.013) | -0.059 (0.013) | 0 (0) | 0 (0) | 0 (0) |
| **State 5** | 0 (0) | 0 (0) | 0 (0) | 0.040 (0.01) | -0.040 (0.01) | 0 (0) | 0 (0) |
| **State 6** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.038 (0.012) | -0.038 (0.012) | 0 (0) |
| **State 7** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.033 (0.012) | -0.033 (0.012) |

Note: The table represents the transitions from row state to column state.
Abbreviations: SE, standard error.

**Table 47: Transition probability matrix at one week for natural history patients (1:1 matching); mean (CI)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 1.000 (1.000, 1.000) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0.039 (0.026, 0.054) | 0.961 (0.946, 0.974) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0.001 (0.001, 0.001) | 0.046 (0.033, 0.062) | 0.953 (0.937, 0.966) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0.001 (0.001, 0.002) | 0.056 (0.038, 0.074) | 0.943 (0.924, 0.961) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0.001 (0.001, 0.002) | 0.038 (0.027, 0.066) | 0.961 (0.932, 0.972) | 0 (0, 0) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.001 (0.000, 0.002) | 0.037 (0.021, 0.064) | 0.963 (0.935, 0.979) | 0 (0, 0) |
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.001 (0.000, 0.001) | 0.032 (0.018, 0.066) | 0.968 (0.932, 0.982) |

Note: The table represents the transitions from row state to column state.
Abbreviations: CI, confidence interval.

### Natural history patients who were matched to 190-203 patients (1:1 matching)

Table 48 provide the transition intensity matrix with SEs for natural history who were matched to 190-203 patients. Table 49 provides the transition probability matrix over a one week time interval for the matched natural history patients who were matched to 190-203 patients,

**Table 48: Transition intensity matrix for natural history patients who were matched to 190-203 patients (1:1 matching); mean (SE)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 2** | 0.037 (0.012) | -0.037 (0.012) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 3** | 0 (0) | 0.053 (0.020) | -0.053 (0.020) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **State 4** | 0 (0) | 0 (0) | 0.062 (0.024) | -0.062 (0.024) | 0 (0) | 0 (0) | 0 (0) |
| **State 5** | 0 (0) | 0 (0) | 0 (0) | 0.065 (0.027) | -0.065 (0.027) | 0 (0) | 0 (0) |

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 6** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.029 (0.014) | -0.029 (0.014) | 0 (0) |
| **State 7** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0.023 (0.011) | -0.023 (0.011) |

Note: The table represents the transitions from row state to column state.
Abbreviations: SE, standard error.

**Table 49: Transition probability matrix at one week for natural history patients who were matched to 190-203 patients (1:1 matching); mean (CI)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 1.000 (1.000, 1.000) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0.036 (0.018, 0.066) | 0.964 (0.934, 0.982) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0.001 (0.000, 0.002) | 0.051 (0.023, 0.088) | 0.948 (0.910, 0.976) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0.002 (0.001, 0.004) | 0.058 (0.025, 0.127) | 0.940 (0.868, 0.974) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0.002 (0.001, 0.005) | 0.061 (0.024, 0.123) | 0.937 (0.874, 0.975) | 0 (0, 0) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.001 (0.000, 0.003) | 0.028 (0.012, 0.075) | 0.971 (0.923, 0.988) | 0 (0, 0) |
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.000 (0.000, 0.001) | 0.023 (0.009, 0.050) | 0.977 (0.948, 0.991) |

Note: The table represents the transitions from row state to column state.
Abbreviations: CI, confidence interval.

### e) Details on model goodness-of-fit assessment, including tables of observed and expected prevalence by health state;

**Cerliponase alfa "all patients" (1:1 matching)**

The observed and expected prevalence by health state for the matched cerliponase alfa "all patients" is given in Table 50 and Table 51, respectively. Additionally,

Figure 38 is a plot of the expected prevalence compared with the observed prevalence of each state.

**Table 50: Observed prevalence by health state for cerliponase alfa "all patients" (1:1 matching)**

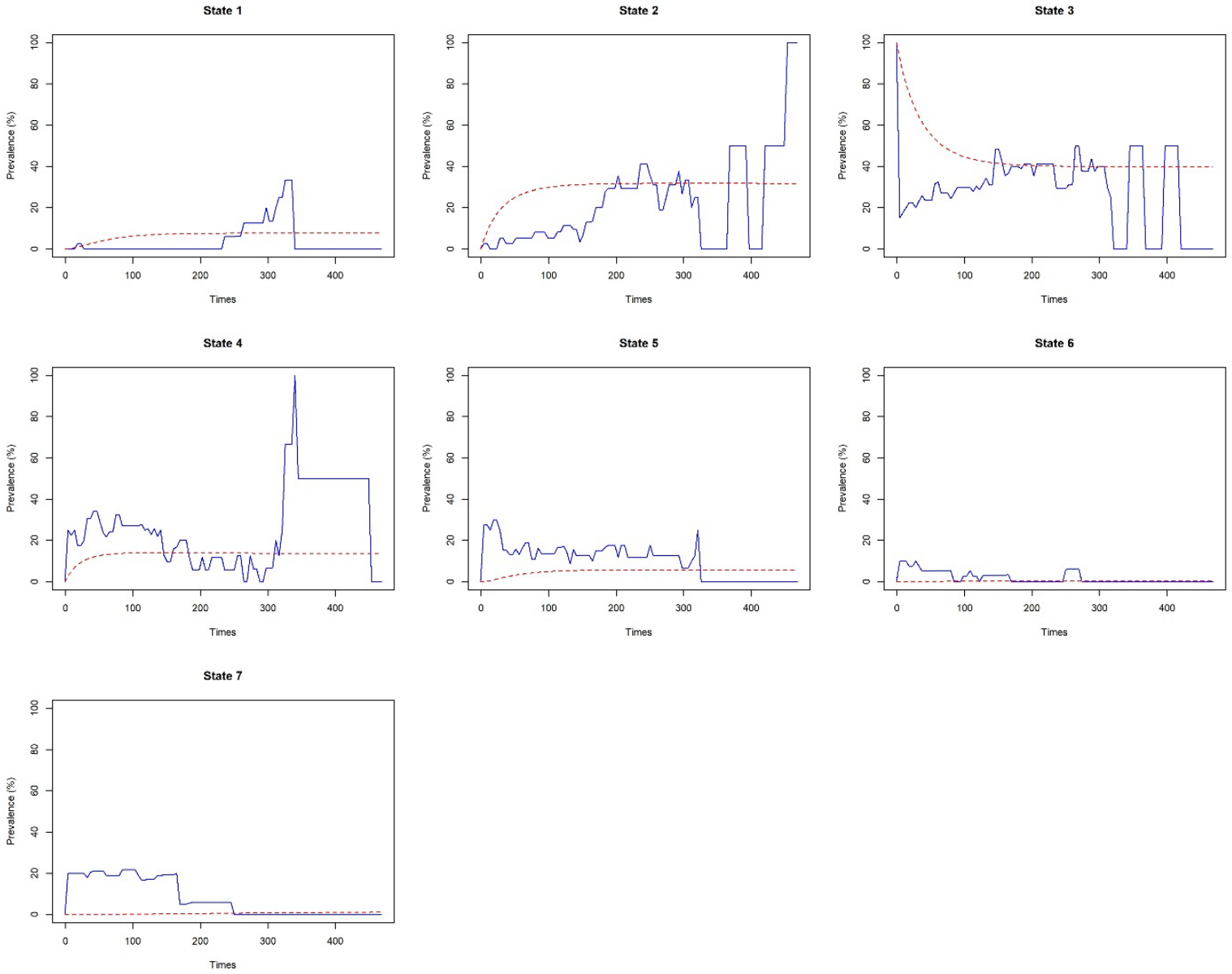
| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 0 (0%) | 2 (5%) | 8 (20%) | 8 (20%) | 10 (25%) | 4 (10%) | 8 (20%) | 40 (100%) |
| 12 | 0 (0%) | 2 (5%) | 9 (24%) | 12 (32%) | 5 (13%) | 2 (5%) | 8 (21%) | 38 (100%) |
| 18 | 0 (0%) | 2 (5%) | 10 (27%) | 12 (32%) | 4 (11%) | 2 (5%) | 7 (19%) | 37 (100%) |
| 24 | 0 (0%) | 1 (3%) | 12 (32%) | 10 (27%) | 5 (14%) | 1 (3%) | 8 (22%) | 37 (100%) |
| 30 | 0 (0%) | 4 (11%) | 12 (34%) | 8 (23%) | 4 (11%) | 1 (3%) | 6 (17%) | 35 (100%) |
| 36 | 0 (0%) | 4 (13%) | 13 (42%) | 3 (10%) | 4 (13%) | 1 (3%) | 6 (19%) | 31 (100%) |
| 42 | 0 (0%) | 5 (25%) | 7 (35%) | 4 (20%) | 3 (15%) | 0 (0%) | 1 (5%) | 20 (100%) |
| 48 | 0 (0%) | 5 (29%) | 7 (41%) | 1 (6%) | 3 (18%) | 0 (0%) | 1 (6%) | 17 (100%) |
| 54 | 1 (6%) | 6 (35%) | 6 (35%) | 1 (6%) | 2 (12%) | 0 (0%) | 1 (6%) | 17 (100%) |
| 60 | 1 (6%) | 5 (31%) | 5 (31%) | 2 (13%) | 2 (13%) | 1 (6%) | 0 (0%) | 16 (100%) |
| 66 | 2 (13%) | 5 (31%) | 6 (38%) | 1 (6%) | 2 (13%) | 0 (0%) | 0 (0%) | 16 (100%) |
| 72 | 2 (20%) | 2 (20%) | 3 (30%) | 2 (20%) | 1 (10%) | 0 (0%) | 0 (0%) | 10 (100%) |
| 78 | 1 (33%) | 0 (0%) | 0 (0%) | 2 (67%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 (100%) |
| 84 | 0 (0%) | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |
| 90 | 0 (0%) | 1 (50%) | 0 (0%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |
| 96 | 0 (0%) | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |
| 102 | 0 (0%) | 1 (50%) | 0 (0%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |

**Table 51: Expected prevalence by health state for cerliponase alfa "all patients" (1:1 matching)**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 0.65 (2%) | 7.32 (18%) | 27.43 (69%) | 3.99 (10%) | 0.6 (1%) | 0.01 (0%) | 0 (0%) | 40 (100%) |
| 12 | 1.44 (4%) | 9.63 (25%) | 20.78 (55%) | 4.86 (13%) | 1.24 (3%) | 0.05 (0%) | 0.01 (0%) | 38 (100%) |
| 18 | 1.98 (5%) | 10.55 (29%) | 17.68 (48%) | 5.06 (14%) | 1.63 (4%) | 0.08 (0%) | 0.03 (0%) | 37 (100%) |

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 24 | 2.34 (6%) | 11.12 (30%) | 16.36 (44%) | 5.16 (14%) | 1.86 (5%) | 0.11 (0%) | 0.06 (0%) | 37 (100%) |
| 30 | 2.42 (7%) | 10.8 (31%) | 14.81 (42%) | 4.9 (14%) | 1.88 (5%) | 0.12 (0%) | 0.09 (0%) | 35 (100%) |
| 36 | 2.25 (7%) | 9.7 (31%) | 12.79 (41%) | 4.33 (14%) | 1.71 (6%) | 0.11 (0%) | 0.1 (0%) | 31 (100%) |
| 42 | 1.49 (7%) | 6.31 (32%) | 8.14 (41%) | 2.79 (14%) | 1.12 (6%) | 0.07 (0%) | 0.09 (0%) | 20 (100%) |
| 48 | 1.28 (8%) | 5.39 (32%) | 6.86 (40%) | 2.36 (14%) | 0.96 (6%) | 0.07 (0%) | 0.09 (1%) | 17 (100%) |
| 54 | 1.29 (8%) | 5.4 (32%) | 6.83 (40%) | 2.36 (14%) | 0.96 (6%) | 0.07 (0%) | 0.1 (1%) | 17 (100%) |
| 60 | 1.22 (8%) | 5.09 (32%) | 6.4 (40%) | 2.21 (14%) | 0.9 (6%) | 0.06 (0%) | 0.11 (1%) | 16 (100%) |
| 66 | 1.23 (8%) | 5.09 (32%) | 6.39 (40%) | 2.21 (14%) | 0.9 (6%) | 0.06 (0%) | 0.12 (1%) | 16 (100%) |
| 72 | 0.77 (8%) | 3.18 (32%) | 3.99 (40%) | 1.38 (14%) | 0.56 (6%) | 0.04 (0%) | 0.08 (1%) | 10 (100%) |
| 78 | 0.23 (8%) | 0.95 (32%) | 1.19 (40%) | 0.41 (14%) | 0.17 (6%) | 0.01 (0%) | 0.03 (1%) | 3 (100%) |
| 84 | 0.15 (8%) | 0.64 (32%) | 0.8 (40%) | 0.27 (14%) | 0.11 (6%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |
| 90 | 0.15 (8%) | 0.64 (32%) | 0.8 (40%) | 0.27 (14%) | 0.11 (6%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |
| 96 | 0.15 (8%) | 0.64 (32%) | 0.79 (40%) | 0.27 (14%) | 0.11 (6%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |
| 102 | 0.15 (8%) | 0.63 (32%) | 0.79 (40%) | 0.27 (14%) | 0.11 (6%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |

**Figure 38: Expected prevalence compared with the observed prevalence of each state for cerliponase alfa "all patients" (1:1 matching)**



### Cerliponase alfa 190-203 patients (1:1 matching)

**The observed and expected prevalence by health state for the matched cerliponase alfa 190-203 is provided in Table 52 and Table 53, respectively. Additionally, a plot of the expected prevalence compared with the observed prevalence of each state is presented in**

Figure 39.

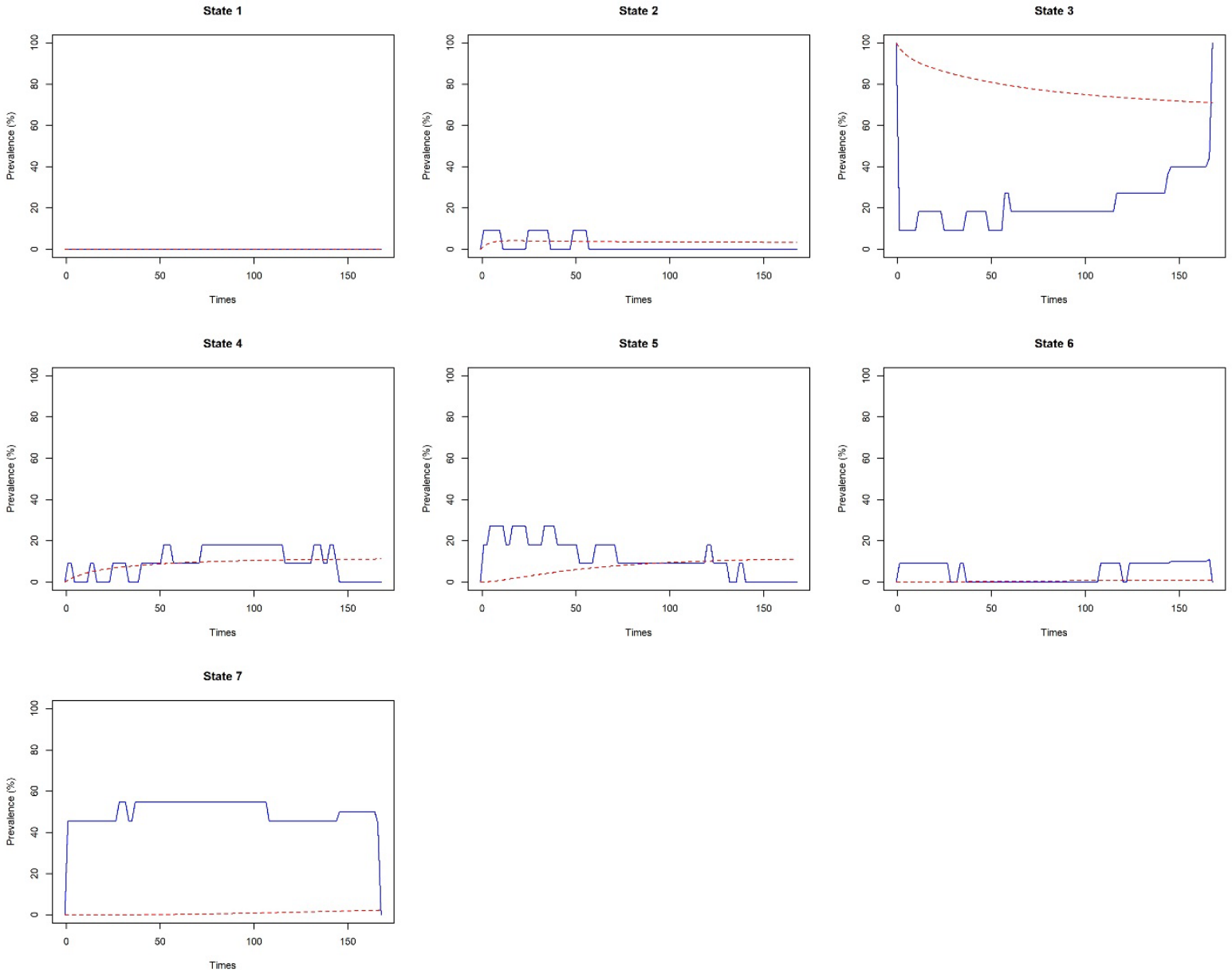
**Table 52: Observed prevalence by health state for cerliponase alfa 190-203 patients (1:1 matching)**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 0 (0%) | 1 (9%) | 1 (9%) | 1 (9%) | 2 (18%) | 1 (9%) | 5 (45%) | 11 (100%) |
| 12 | 0 (0%) | 1 (9%) | 1 (9%) | 2 (18%) | 1 (9%) | 0 (0%) | 6 (55%) | 11 (100%) |
| 18 | 0 (0%) | 0 (0%) | 2 (18%) | 2 (18%) | 1 (9%) | 0 (0%) | 6 (55%) | 11 (100%) |
| 24 | 0 (0%) | 0 (0%) | 2 (18%) | 2 (18%) | 1 (9%) | 0 (0%) | 6 (55%) | 11 (100%) |
| 30 | 0 (0%) | 0 (0%) | 3 (27%) | 1 (9%) | 1 (9%) | 1 (9%) | 5 (45%) | 11 (100%) |
| 36 | 0 (0%) | 0 (0%) | 4 (40%) | 0 (0%) | 0 (0%) | 1 (10%) | 5 (50%) | 10 (100%) |

**Table 53: Expected prevalence by health state for cerliponase alfa 190-203 patients (1:1 matching)**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 0 (0%) | 0.45 (4%) | 9.44 (86%) | 0.76 (7%) | 0.34 (3%) | 0.01 (0%) | 0 (0%) | 11 (100%) |
| 12 | 0 (0%) | 0.42 (4%) | 8.86 (81%) | 0.98 (9%) | 0.69 (6%) | 0.04 (0%) | 0.02 (0%) | 11 (100%) |
| 18 | 0 (0%) | 0.4 (4%) | 8.47 (77%) | 1.09 (10%) | 0.92 (8%) | 0.06 (1%) | 0.06 (1%) | 11 (100%) |
| 24 | 0 (0%) | 0.39 (4%) | 8.2 (75%) | 1.16 (11%) | 1.06 (10%) | 0.08 (1%) | 0.11 (1%) | 11 (100%) |
| 30 | 0 (0%) | 0.38 (3%) | 8.01 (73%) | 1.2 (11%) | 1.15 (10%) | 0.09 (1%) | 0.17 (2%) | 11 (100%) |
| 36 | 0 (0%) | 0.34 (3%) | 7.15 (72%) | 1.11 (11%) | 1.1 (11%) | 0.09 (1%) | 0.21 (2%) | 10 (100%) |

**Figure 39: Expected prevalence compared with the observed prevalence of each state for the 190-203 patients**



**Cerliponase alfa “all patients” (1:1 matching) piecewise at 6 months**

The observed and expected prevalence by health state for the matched cerliponase alfa “all patients” piecewise at 6 months is presented in Table 54 and Table 55, respectively. Additionally,

Figure 40 is a plot of the expected prevalence compared with the observed prevalence of each state.

**Table 54: Observed prevalence by health state for cerliponase alfa "all patients" (1:1 matching) piecewise at 6 months**

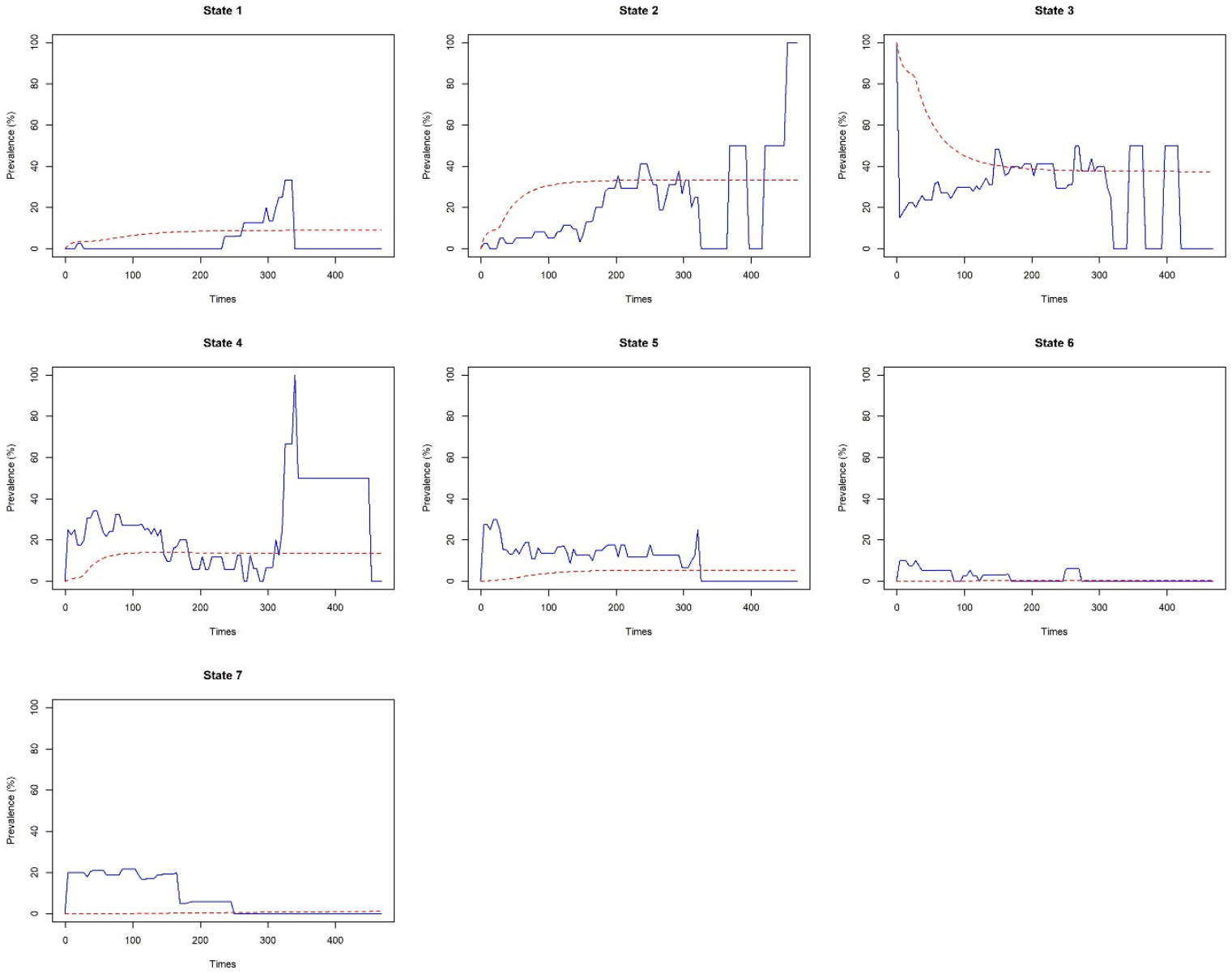
| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 0 (0%) | 2 (5%) | 8 (20%) | 8 (20%) | 10 (25%) | 4 (10%) | 8 (20%) | 40 (100%) |
| 12 | 0 (0%) | 2 (5%) | 9 (24%) | 12 (32%) | 5 (13%) | 2 (5%) | 8 (21%) | 38 (100%) |
| 18 | 0 (0%) | 2 (5%) | 10 (27%) | 12 (32%) | 4 (11%) | 2 (5%) | 7 (19%) | 37 (100%) |
| 24 | 0 (0%) | 1 (3%) | 12 (32%) | 10 (27%) | 5 (14%) | 1 (3%) | 8 (22%) | 37 (100%) |
| 30 | 0 (0%) | 4 (11%) | 12 (34%) | 8 (23%) | 4 (11%) | 1 (3%) | 6 (17%) | 35 (100%) |
| 36 | 0 (0%) | 4 (13%) | 13 (42%) | 3 (10%) | 4 (13%) | 1 (3%) | 6 (19%) | 31 (100%) |
| 42 | 0 (0%) | 5 (25%) | 7 (35%) | 4 (20%) | 3 (15%) | 0 (0%) | 1 (5%) | 20 (100%) |
| 48 | 0 (0%) | 5 (29%) | 7 (41%) | 1 (6%) | 3 (18%) | 0 (0%) | 1 (6%) | 17 (100%) |
| 54 | 1 (6%) | 6 (35%) | 6 (35%) | 1 (6%) | 2 (12%) | 0 (0%) | 1 (6%) | 17 (100%) |
| 60 | 1 (6%) | 5 (31%) | 5 (31%) | 2 (13%) | 2 (13%) | 1 (6%) | 0 (0%) | 16 (100%) |
| 66 | 2 (13%) | 5 (31%) | 6 (38%) | 1 (6%) | 2 (13%) | 0 (0%) | 0 (0%) | 16 (100%) |
| 72 | 2 (20%) | 2 (20%) | 3 (30%) | 2 (20%) | 1 (10%) | 0 (0%) | 0 (0%) | 10 (100%) |
| 78 | 1 (33%) | 0 (0%) | 0 (0%) | 2 (67%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 (100%) |
| 84 | 0 (0%) | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |
| 90 | 0 (0%) | 1 (50%) | 0 (0%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |
| 96 | 0 (0%) | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |
| 102 | 0 (0%) | 1 (50%) | 0 (0%) | 1 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (100%) |

**Table 55: Expected prevalence by health state for cerliponase alfa "all patients" (1:1 matching) piecewise at 6 months**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 1.42 (4%) | 3.74 (9%) | 33.7 (84%) | 0.86 (2%) | 0.28 (1%) | 0.01 (0%) | 0 (0%) | 40 (100%) |
| 12 | 1.56 (4%) | 8.69 (23%) | 23.1 (61%) | 3.98 (10%) | 0.64 (2%) | 0.02 (0%) | 0.01 (0%) | 38 (100%) |
| 18 | 2.01 (5%) | 10.53 (28%) | 18.47 (50%) | 4.81 (13%) | 1.12 (3%) | 0.04 (0%) | 0.02 (0%) | 37 (100%) |

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 24 | 2.44 (7%) | 11.44 (31%) | 16.46 (44%) | 5.08 (14%) | 1.48 (4%) | 0.06 (0%) | 0.04 (0%) | 37 (100%) |
| 30 | 2.6 (7%) | 11.22 (32%) | 14.56 (42%) | 4.86 (14%) | 1.61 (5%) | 0.08 (0%) | 0.06 (0%) | 35 (100%) |
| 36 | 2.48 (8%) | 10.12 (33%) | 12.4 (40%) | 4.3 (14%) | 1.54 (5%) | 0.08 (0%) | 0.08 (0%) | 31 (100%) |
| 42 | 1.67 (8%) | 6.59 (33%) | 7.81 (39%) | 2.77 (14%) | 1.03 (5%) | 0.06 (0%) | 0.07 (0%) | 20 (100%) |
| 48 | 1.46 (9%) | 5.63 (33%) | 6.54 (38%) | 2.34 (14%) | 0.89 (5%) | 0.05 (0%) | 0.07 (0%) | 17 (100%) |
| 54 | 1.49 (9%) | 5.65 (33%) | 6.49 (38%) | 2.33 (14%) | 0.9 (5%) | 0.05 (0%) | 0.09 (1%) | 17 (100%) |
| 60 | 1.41 (9%) | 5.33 (33%) | 6.07 (38%) | 2.19 (14%) | 0.85 (5%) | 0.05 (0%) | 0.1 (1%) | 16 (100%) |
| 66 | 1.42 (9%) | 5.33 (33%) | 6.05 (38%) | 2.18 (14%) | 0.85 (5%) | 0.05 (0%) | 0.11 (1%) | 16 (100%) |
| 72 | 0.89 (9%) | 3.33 (33%) | 3.77 (38%) | 1.36 (14%) | 0.53 (5%) | 0.03 (0%) | 0.08 (1%) | 10 (100%) |
| 78 | 0.27 (9%) | 1 (33%) | 1.13 (38%) | 0.41 (14%) | 0.16 (5%) | 0.01 (0%) | 0.03 (1%) | 3 (100%) |
| 84 | 0.18 (9%) | 0.67 (33%) | 0.75 (38%) | 0.27 (14%) | 0.11 (5%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |
| 90 | 0.18 (9%) | 0.67 (33%) | 0.75 (38%) | 0.27 (14%) | 0.11 (5%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |
| 96 | 0.18 (9%) | 0.67 (33%) | 0.75 (37%) | 0.27 (14%) | 0.11 (5%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |
| 102 | 0.18 (9%) | 0.67 (33%) | 0.75 (37%) | 0.27 (14%) | 0.11 (5%) | 0.01 (0%) | 0.02 (1%) | 2 (100%) |

**Figure 40: Expected prevalence compared with the observed prevalence of each state for cerliponase alfa "all patients" (1:1 matching) piecewise at 6 months**



**Natural history patients (1:1 matching)**

The observed and expected prevalence by health state for the matched natural history patients is given in Table 56 and Table 57, respectively. Additionally,

Figure 41 is a plot of the expected prevalence compared with the observed prevalence of each state.

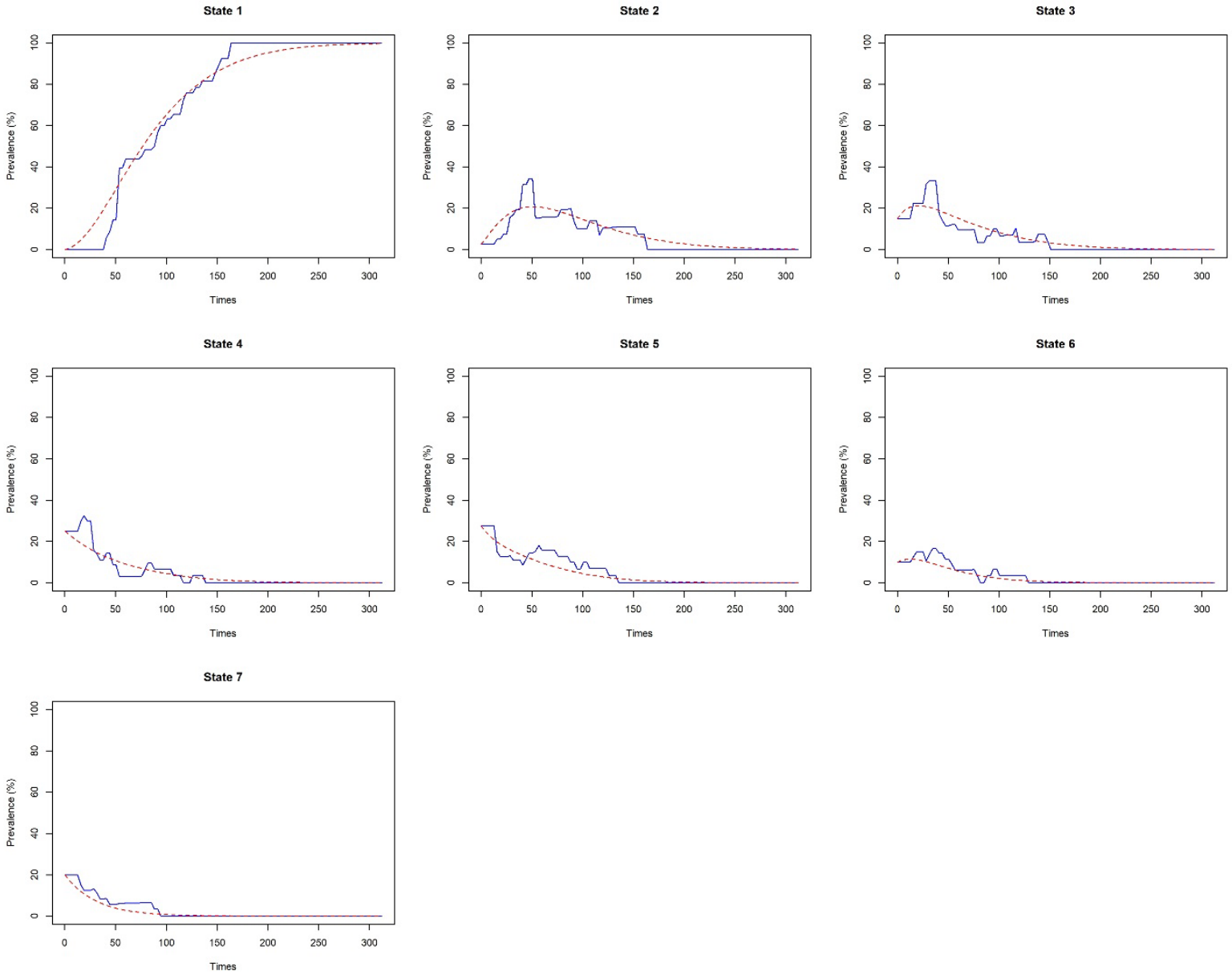
**Table 56: Observed prevalence by health state for the natural history patients (1:1 matching)**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 0 (0%) | 6 (16%) | 12 (32%) | 6 (16%) | 5 (13%) | 4 (11%) | 5 (13%) | 38 (100%) |
| 12 | 13 (39%) | 5 (15%) | 4 (12%) | 1 (3%) | 5 (15%) | 3 (9%) | 2 (6%) | 33 (100%) |
| 18 | 15 (48%) | 6 (19%) | 1 (3%) | 2 (6%) | 4 (13%) | 1 (3%) | 2 (6%) | 31 (100%) |
| 24 | 19 (63%) | 3 (10%) | 2 (7%) | 2 (7%) | 3 (10%) | 1 (3%) | 0 (0%) | 30 (100%) |
| 30 | 22 (79%) | 3 (11%) | 1 (4%) | 1 (4%) | 1 (4%) | 0 (0%) | 0 (0%) | 28 (100%) |
| 36 | 25 (93%) | 2 (7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |
| 42 | 27 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |
| 48 | 27 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |
| 54 | 27 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |
| 60 | 27 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |
| 66 | 27 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |
| 72 | 27 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |

**Table 57: Expected prevalence by health state for the natural history patients (1:1 matching)**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 3.99 (10%) | 6.36 (17%) | 7.99 (21%) | 6.08 (16%) | 6.33 (17%) | 4 (11%) | 3.26 (9%) | 38 (100%) |
| 12 | 10.08 (31%) | 6.85 (21%) | 5.52 (17%) | 3.43 (10%) | 3.66 (11%) | 2.25 (7%) | 1.21 (4%) | 33 (100%) |
| 18 | 15.78 (51%) | 5.67 (18%) | 3.64 (12%) | 2.09 (7%) | 2.17 (7%) | 1.17 (4%) | 0.48 (2%) | 31 (100%) |
| 24 | 20.24 (67%) | 4.17 (14%) | 2.33 (8%) | 1.25 (4%) | 1.23 (4%) | 0.58 (2%) | 0.2 (1%) | 30 (100%) |
| 30 | 22.26 (80%) | 2.72 (10%) | 1.36 (5%) | 0.68 (2%) | 0.63 (2%) | 0.26 (1%) | 0.08 (0%) | 28 (100%) |
| 36 | 23.67 (88%) | 1.71 (6%) | 0.78 (3%) | 0.36 (1%) | 0.32 (1%) | 0.12 (0%) | 0.03 (0%) | 27 (100%) |
| 42 | 25.07 (93%) | 1.06 (4%) | 0.44 (2%) | 0.19 (1%) | 0.16 (1%) | 0.06 (0%) | 0.01 (0%) | 27 (100%) |
| 48 | 25.92 (96%) | 0.63 (2%) | 0.24 (1%) | 0.1 (0%) | 0.08 (0%) | 0.03 (0%) | 0.01 (0%) | 27 (100%) |
| 54 | 26.42 (98%) | 0.36 (1%) | 0.13 (0%) | 0.05 (0%) | 0.04 (0%) | 0.01 (0%) | 0 (0%) | 27 (100%) |
| 60 | 26.69 (99%) | 0.2 (1%) | 0.06 (0%) | 0.02 (0%) | 0.02 (0%) | 0.01 (0%) | 0 (0%) | 27 (100%) |
| 66 | 26.84 (99%) | 0.1 (0%) | 0.03 (0%) | 0.01 (0%) | 0.01 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |
| 72 | 26.92 (100%) | 0.05 (0%) | 0.02 (0%) | 0.01 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 27 (100%) |

**Figure 41: Expected prevalence compared with the observed prevalence of each state for the natural history patients (1:1 matching)**



**Natural history patients who were matched to 190-203 patients (1:1 matching)**

The observed and expected prevalence by health state for the matched natural history patients who were matched to 190-203 patients is provided in Table 58 and Table 59, respectively. Additionally,

Figure 42 is a plot of the expected prevalence compared with the observed prevalence of each state.

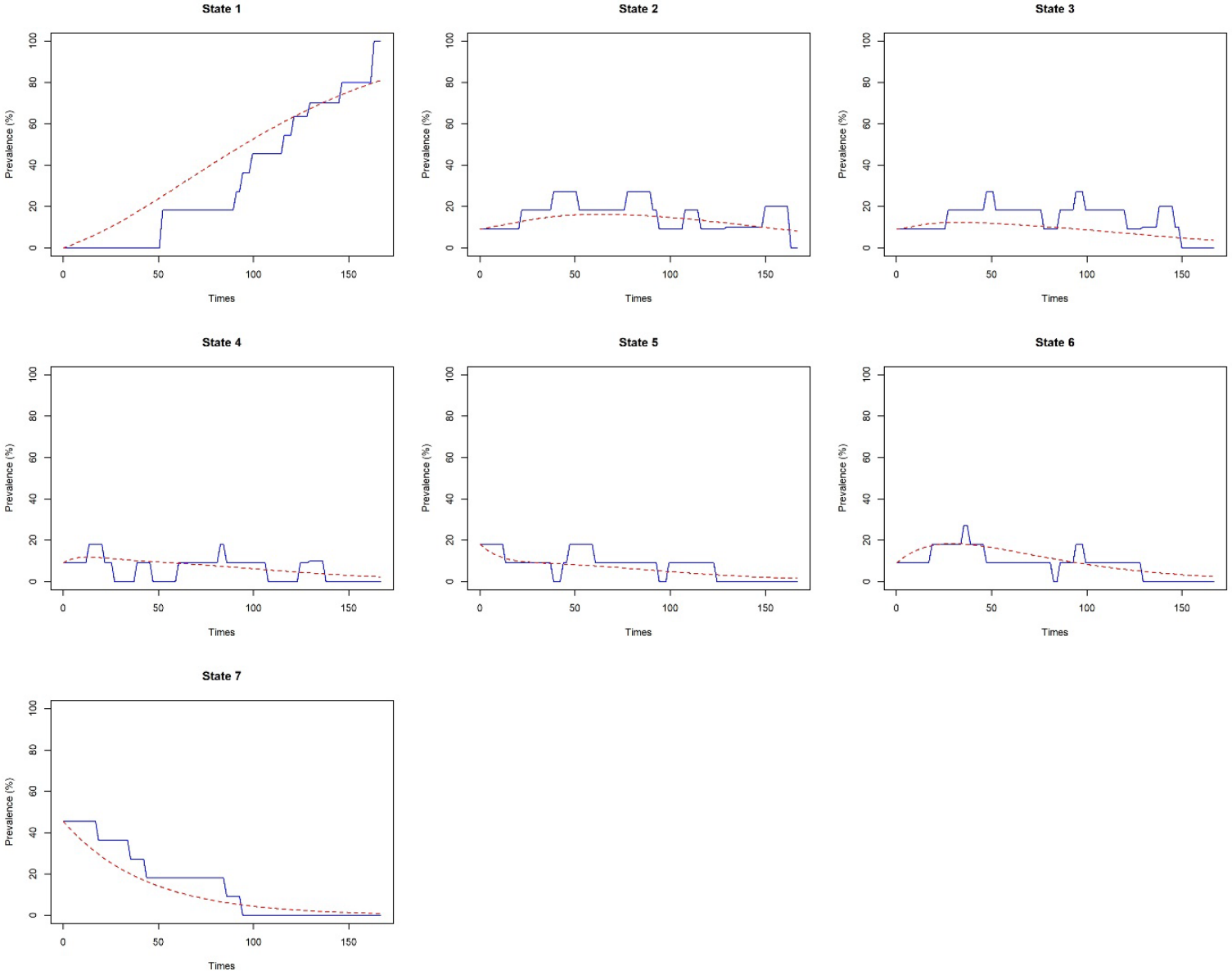
**Table 58: Observed prevalence by health state for the natural history patients who were matched to 190-203 patients (1:1 matching)**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 0 (0%) | 2 (18%) | 2 (18%) | 0 (0%) | 1 (9%) | 2 (18%) | 4 (36%) | 11 (100%) |
| 12 | 2 (18%) | 2 (18%) | 2 (18%) | 0 (0%) | 2 (18%) | 1 (9%) | 2 (18%) | 11 (100%) |
| 18 | 2 (18%) | 3 (27%) | 1 (9%) | 1 (9%) | 1 (9%) | 1 (9%) | 2 (18%) | 11 (100%) |
| 24 | 5 (45%) | 1 (9%) | 2 (18%) | 1 (9%) | 1 (9%) | 1 (9%) | 0 (0%) | 11 (100%) |
| 30 | 7 (70%) | 1 (10%) | 1 (10%) | 1 (10%) | 0 (0%) | 0 (0%) | 0 (0%) | 10 (100%) |
| 36 | 8 (80%) | 2 (20%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 10 (100%) |
| 42 | 10 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 10 (100%) |

**Table 59: Expected prevalence by health state for the natural history patients who were matched to 190-203 patients (1:1 matching)**

| Months | State.1; n (%) | State.2; n (%) | State.3; n (%) | State.4; n (%) | State.5; n (%) | State.6; n (%) | State.7; n (%) | Total; n (%) |
|---|---|---|---|---|---|---|---|---|
| 6 | 1.17 (11%) | 1.48 (13%) | 1.35 (12%) | 1.22 (11%) | 1.03 (9%) | 2.01 (18%) | 2.74 (25%) | 11 (100%) |
| 12 | 2.74 (25%) | 1.76 (16%) | 1.3 (12%) | 1.03 (9%) | 0.89 (8%) | 1.78 (16%) | 1.49 (14%) | 11 (100%) |
| 18 | 4.43 (40%) | 1.76 (16%) | 1.14 (10%) | 0.86 (8%) | 0.71 (6%) | 1.3 (12%) | 0.81 (7%) | 11 (100%) |
| 24 | 6.03 (55%) | 1.58 (14%) | 0.93 (8%) | 0.65 (6%) | 0.5 (5%) | 0.86 (8%) | 0.44 (4%) | 11 (100%) |
| 30 | 6.74 (67%) | 1.2 (12%) | 0.63 (6%) | 0.41 (4%) | 0.3 (3%) | 0.49 (5%) | 0.22 (2%) | 10 (100%) |
| 36 | 7.75 (78%) | 0.93 (9%) | 0.44 (4%) | 0.27 (3%) | 0.19 (2%) | 0.3 (3%) | 0.12 (1%) | 10 (100%) |
| 42 | 8.51 (85%) | 0.67 (7%) | 0.29 (3%) | 0.17 (2%) | 0.11 (1%) | 0.18 (2%) | 0.07 (1%) | 10 (100%) |

**Figure 42: Expected prevalence compared with the observed prevalence of each state for the natural history patients who were matched to 190-203 patients (1:1 matching)**



### f) Whether any convergence issues arose and how these were dealt with;

The five models implemented in the 'msm' package converged.

### g) Provide mean sojourn times in each health state and probability that each state is next by treatment group;

**Cerliponase alfa "all patients" (1:1 matching)**

Table 60 shows the mean sojourn times in weeks in each health state for the matched cerliponase alfa "all patients". Table 61 shows the probability that each state is next for the matched cerliponase alfa "all patients".

**Table 60: Mean sojourn times (in weeks) in each health state for cerliponase alfa "all patients" (1:1 matching)**

| | Mean (SE) | (LCL, UCL) |
|---|---|---|
| State 1 | 31.93 (17.38) | (10.99, 92.82) |
| State 2 | 47.45 (11.07) | (30.03, 74.96) |
| State 3 | 57.51 (9.52) | (41.57, 79.55) |
| Start 4 | 31.86 (4.95) | (23.49, 43.20) |
| State 5 | 30.40 (5.41) | (21.45, 43.09) |
| State 6 | 20.96 (6.50) | (11.42, 38.48) |
| State 7 | 295.61 (148.37) | (110.53, 790.57) |

Abbreviations: LCL, lower confidence level; SE, standard error; UCL, upper confidence level.

**Table 61: Probability that each state is next for cerliponase alfa "all patients" (1:1 matching); mean (LCL, UCL)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0, 0) | 1.000 (1.000, 1.000) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0.359 (0.178, 0.583) | 0 (0, 0) | 0.641 (0.417, 0.822) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0 (0, 0) | 0.620 (0.461, 0.768) | 0 (0, 0) | 0.380 (0.232, 0.539) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0 (0, 0) | 0.605 (0.464, 0.746) | 0 (0, 0) | 0.395 (0.254, 0.536) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.908 (0.757, 0.969) | 0 (0, 0) | 0.092 (0.031, 0.243) | 0 (0, 0) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.726 (0.412, 0.916) | 0 (0, 0) | 0.274 (0.084, 0.588) |
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.000 (1.000, 1.000) | 0 (0, 0) |

Note: The table represents the transitions from row state to column state.
Abbreviations: LCL, lower confidence level; UCL, upper confidence level.

### Cerliponase alfa 190-203 patients (1:1 matching)

Table 62 shows the mean sojourn times in weeks in each health state for the matched cerliponase alfa 190-203 patients. Table 63 shows the probability that each state is next for the matched cerliponase alfa “all patients”.

**Table 62: Mean sojourn times (in weeks) in each health state for cerliponase alfa 190-203 patients (1:1 matching)**

| | **Mean (SE)** | **(LCL, UCL)** |
|---|---|---|
| State 1 | NA | NA |
| State 2 | 4.46 (3.17) | (1.11, 17.95) |
| State 3 | 61.50 (35.52) | (19.83, 190.74) |
| Start 4 | 14.26 (4.59) | (7.59, 26.80) |
| State 5 | 25.89 (9.30) | (12.80, 52.36) |
| State 6 | 17.35 (8.82) | (6.41, 46.97) |
| State 7 | 404.52 (288.11) | (100.16, 1633.77) |

Abbreviations: LCL, lower confidence level; NA, not applicable; SE, standard error; UCL, upper confidence level.

**Table 63: Probability that each state is next for cerliponase alfa 190-203 patients (1:1 matching); mean (LCL, UCL)**

| **To**<br>**From** | **State 1** | **State 2** | **State 3** | **State 4** | **State 5** | **State 6** | **State 7** |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0 (0, 0) | 0 (0, 0) | 1.000 (1.000, 1.000) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0 (0, 0) | 0.646 (0.190, 0.930) | 0 (0, 0) | 0.354 (0.070, 0.810) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0 (0, 0) | 0.469 (0.199, 0.758) | 0 (0, 0) | 0.531 (0.242, 0.801) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.882 (0.484, 0.984) | 0 (0, 0) | 0.118 (0.016, 0.516) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.480 (0.108, 0.868) | 0 (0, 0) | 0.520 (0.132, 0.892) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.000 (1.000, 1.000) | 0 (0, 0) |

Note: The table represents the transitions from row state to column state.
Abbreviations: LCL, lower confidence level; UCL, upper confidence level.

### Cerliponase alfa "all patients" (1:1 matching) piecewise at 6 months

Table 64 shows the mean sojourn times in weeks in each health state for the matched cerliponase alfa "all patients" piecewise at 6 months. Table 65 shows the probability that each state is next for the matched cerliponase alfa "all patients" piecewise at 6 months.

**Table 64: Mean sojourn times (in weeks) in each health state for cerliponase alfa "all patients" (1:1 matching) piecewise at 6 months**

| | **Mean (SE)** | **(LCL, UCL)** |
|---|---|---|
| State 1 | 27.77 (16.93) | (8.41, 91.73) |
| State 2 | 35.70 ( 9.01) | (21.77, 58.55) |
| State 3 | 58.31 (17.21) | (32.70, 103.98) |
| Start 4 | 33.22 ( 5.25) | (24.37, 45.28) |
| State 5 | 34.08 ( 6.76) | (23.10, 50.26) |
| State 6 | 21.93 ( 7.28) | (11.44, 42.03) |
| State 7 | 295.94 (150.46) | (109.26, 801.59) |

Abbreviations: LCL, lower confidence level; SE, standard error; UCL, upper confidence level.

**Table 65: Probability that each state is next for cerliponase alfa "all patients" (1:1 matching) piecewise at 6 months; mean (LCL, UCL)**

| **To**<br>**From** | **State 1** | **State 2** | **State 3** | **State 4** | **State 5** | **State 6** | **State 7** |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0, 0) | 1.000 (1.000, 1.000) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 0.364 (0.166, 0.627) | 0 (0, 0) | 0.636 (0.373, 0.834) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0 (0, 0) | 0.677 (0.320, 0.914) | 0 (0, 0) | 0.323 (0.086, 0.680) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0 (0, 0) | 0.627 (0.470, 0.757) | 0 (0, 0) | 0.373 (0.243, 0.530) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.905 (0.725, 0.971) | 0 (0, 0) | 0.095 (0.029, 0.275) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.700 (0.376, 0.900) | 0 (0, 0) | 0.300 (0.100, 0.624) |

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.000 (1.000, 1.000) | 0 (0, 0) |

Note: The table represents the transitions from row state to column state.
Abbreviations: LCL, lower confidence level; UCL, upper confidence level.

### Natural history patients (1:1 matching)

Table 66 shows the mean sojourn times in weeks in each health state for the matched natural history patients. Table 67 shows the probability that each state is next for the matched natural history patients.

**Table 66: Mean sojourn times (in weeks) in each health state for the matched natural history patients (1:1 matching)**

| | Mean (SE) | (LCL, UCL) |
|---|---|---|
| State 1 | Absorbing state | Absorbing state |
| State 2 | 25.35 (5.27) | (16.87, 38.08) |
| State 3 | 20.63 (4.21) | (13.83, 30.76) |
| Start 4 | 17.02 (3.68) | (11.14, 26.01) |
| State 5 | 25.15 (6.16) | (15.57, 40.65) |
| State 6 | 26.26 (8.53) | (13.90, 49.62) |
| State 7 | 30.53 (11.12) | (14.95, 62.32) |

Abbreviations: LCL, lower confidence level; SE, standard error; UCL, upper confidence level.

**Table 67: Probability that each state is next for the natural history patients (1:1 matching); mean (LCL, UCL)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) |

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) |

Note: The table represents the transitions from row state to column state.
Abbreviations: LCL, lower confidence level; UCL, upper confidence level.

### Natural history patients who were matched to 190-203 patients (1:1 matching)

Table 68 shows the mean sojourn times in weeks in each health state for the matched natural history patients who were matched to 190-203 patients. Table 69 shows the probability that each state is next for the matched natural history patients who were matched to 190-203 patients.

**Table 68: Mean sojourn times (in weeks) in each health state for the matched natural history patients who were matched to 190-203 patients.**

| | Mean (SE) | (LCL, UCL) |
|---|---|---|
| State 1 | Absorbing state | Absorbing state |
| State 2 | 27.34 (9.22) | (14.12, 52.94) |
| State 3 | 18.85 (6.98) | (9.12, 38.96) |
| Start 4 | 16.16 (6.23) | (7.59, 34.38) |
| State 5 | 15.49 (6.49) | (6.82, 35.20) |
| State 6 | 34.47 (16.07) | (13.83, 85.94) |
| State 7 | 42.88 (19.54) | (17.55, 104.76) |

Abbreviations: LCL, lower confidence level; SE, standard error; UCL, upper confidence level.

**Table 69: Probability that each state is next for the natural history patients who were matched to 190-203 patients (1:1 matching); mean (LCL, UCL)**

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 1** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 2** | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 3** | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 4** | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 5** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) |
| **State 6** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) | 0 (0, 0) |

| To<br>From | State 1 | State 2 | State 3 | State 4 | State 5 | State 6 | State 7 |
|---|---|---|---|---|---|---|---|
| **State 7** | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 1.00 (1,00, 1.00) | 0 (0, 0) |

Note: The table represents the transitions from row state to column state.
Abbreviations: LCL, lower confidence level; UCL, upper confidence level.

**h) Numbers, percentages and plots with observed and expected prevalence by health state for each treatment group.**

See B2.e for the numbers, percentages and plots with observed and expected prevalence by health state for each treatment group.

**i) Provide information on how the piecewise model was specified. How was the time at which the covariates change chosen? Provide details on the piecewise model, number of observations used to inform transitions, model's goodness-of-fit and the results including precision estimates (e.g. confidence intervals)**

Details for how the piecewise model was chosen and results are provided in the corresponding section in B2.

**j) Elements a) to h) should be provided for transition probabilities estimated on the following datasets matched to study 190-901: i) study 190-203 and ii) 'all patients'.**

The relevant outputs have been provided in the relevant sections of B2 above.

## B3. Priority question: The parameter uncertainty of the transition probabilities was modelled independently for each transition. Please provide the following elements:

**a) Detail how were the confidence intervals for each transition probability estimated in health states 1 to 7 (e.g., were these informed by the MSM R package analysis?) and confirm if the confidence interval estimates in the economic model (Control sheet) are correct (if not, please report the correct figures);**

Confidence intervals for the transition intensities are calculated by the MSM R package from the covariance matrix of the estimates by assuming the distribution is symmetric on the log scale. Transition intensities were converted into probabilities for use in the cost-effectiveness

model using the exponential model. Minor errors have been identified in the confidence intervals for the transition intensities informed by Study 190-203; these have been corrected in the updated cost-effectiveness model shared alongside this response.

**b) Justify why is there no correlation structure relating the uncertainty of jointly estimated transition probabilities (i.e., why was the variance-covariance matrix from the msn estimation not used to obtain correlated draws for these parameters?). If feasible this should be implemented in the economic model by the company.**

Covariance matrices for the transition intensities were outputted from the MSM R package. However, implementation of the multivariate normal distribution using these covariance matrices resulted in negative transition intensities. It was therefore not possible to generate correlated draws of the transition intensities.

Although this represents a limitation of the cost-effectiveness model, the current approach is expect to overestimate decision uncertainty, and is therefore expected to be conservative.

**B4. Priority question: Please contrast and compare the approach taken to estimate transition probabilities for health states 1 to 7 in the original HST12 and the current review. The EAG is particularly interested in the following aspects:**

**a) Use of MSM package vs. the original HST12 approach (estimated using the method preferred by the NICE committee). Please detail the rationale for the use of a different estimation method in the current appraisal and provide the information to populate the table illustrated below with number of events and person-time in health state to reflect time at risk for each transition;**

The MSM approach was used in order to account for:

- Multiple data sources, with differing observation intervals
- Differing durations of follow-up between patients.
- Transitions that were intermittently observed in time.

The number of events for each transition is presented in Table 70. Please see B2.g for the mean sojurn times in each health state.

**Table 70: Number of events in each health state**

| | Number of events | | | |
|---|---|---|---|---|
| **Transition** | **Study 190-203 matched to study190-901** | | **All patients pooled dataset matched to study 190-901** | |
| | **CP** | **SoC** | **CP** | **SoC** |
| **HS7 to HS6** | 0 | 0 | 5 | 0 |
| **HS6 to HS7** | 0 | 10 | 7 | 27 |
| **HS6 to HS5** | 3 | 0 | 15 | 0 |
| **HS5 to HS6** | 2 | 9 | 25 | 29 |
| **HS5 to HS4** | 2 | 0 | 16 | 0 |
| **HS4 to HS5** | 5 | 8 | 31 | 27 |
| **HS4 to HS3** | 5 | 0 | 17 | 0 |
| **HS3 to HS4** | 7 | 7 | 30 | 19 |
| **HS3 to HS2** | 1 | 0 | 3 | 0 |
| **HS2 to HS3** | 2 | 5 | 8 | 11 |
| **HS2 to HS1** | 2 | 0 | 3 | 0 |
| **HS1 to HS2** | 2 | 5 | 4 | 8 |

Abbreviations: CP, cerliponase alfa; HS, health state; SoC, standard of care.

**b) Please provide the information to populate the table illustrated below with number of events and person-time in health state to reflect time at risk for each transition using the data available at the time of the original HST12 (i.e., study 190-201/2 matched to study 190-901 data cut used to inform the original HST12);**

It was not possible to access the original HST12 dataset in the two-week period, therefore this question could not be answered. The BioMarin BioStats team will re-analyse the data and provide the person-time in health state information as soon as possible.

| Transition | | Number of events (person-time in health state) | |
|---|---|---|---|
| | | Study 190-201/2 matched to study 190-901 | |
| | | CP | SoC |
| HS 6 and 7 | Improve | | |
| | Maintain | | |
| | Decline | | |
| HS 3, 4 and 5 | Improve | | |
| | Maintain | | |
| | Decline | | |
| HS 1 and 2 | Improve | | |
| | Maintain | | |
| | Decline | | |

Abbreviations: CP, cerliponase alfa; HS, health state; SoC, standard of care.

### c) Estimation of transition probabilities by individual health state vs. by aggregated health states (1-2, 3-5 and 6-7). Please comment on whether evidence challenges that led to the decision to assume similar probabilities across some health states in the original HST12 were resolved under current evidence levels.

In the analyses conducted for this resubmission, transition intensities were estimated for each individual transition; given the models converged and the estimates were considered to be plausible. Therefore, it was not considered necessary to estimate transitions for aggregated health states.

### d) Assumptions on patient stabilisation and evidence supporting the assumptions applied in the current appraisal.

A summary of the stabilisation assumptions for each of the original company submission in HST12, the decision-making model in HST12, and the current resubmission are presented in Table 71.

At the time of the original submission, trial data suggested that all patients may be expected to stabilise (either at 16 or 96 weeks). Following further data collection, it is no longer expected that all cerliponase alfa patients will stabilise irrespective of starting state. However, evidence from five patients who enrolled in Study 190-203 and transitioned into Study 190-504 demonstrates no decline in ML score in the first 6 years for patients who initiated treatment with a baseline ML score of 6, and were aged under 3 years. Of the other two patients who initiated treatment with a baseline ML score of 6, and aged under 3 years

(but did not transition into Study 190-504), both patients remained at an ML score of 6 for the duration of available follow-up.

**Table 71: Stabilisation assumptions**

| Analysis | Modelled stabilisation assumptions | Rationale |
|---|---|---|
| Original company submission for HST12 | 'Early stabilisers' are assumed to remain in the same health state from 16 weeks until the end of the model time horizon<br>'Late stabilisers' are assumed to progress at a rate of 1 point on the ML scale between 16 and 96 weeks, after which they remain in the same health state until the end of the model time horizon | This was in line with what was observed in the clinical trial, where 6 patients were seen to progress 1 more point on the ML scale between 16 and 96 weeks, and 17 patients continued to stay at the same score. |
| Decision-making model for HST12 | 'Early stabilisers' are assumed to remain in the same health state from 16 weeks | The committee assumed 'partial stabilisation' (i.e. stabilisation for early stabilisers only) given the uncertainty around whether cerliponase alfa patients may be expected to stabilise. |
| Current resubmission | Patients starting treatment in health state 1 (ML score of 6) remain in this state for the first 6 years<br>After this, these patients are modelled to transition between health states at half the rate observed for patients initiating treatment in other health states | In the population of patients who entered Study 190-203 at less than 3 years of age, seven patients initiated treatment at an ML score of 6, and one patient initiated treatment at an ML score of 5.<br>Of the patients who initiated treatment with an ML score of 6 and transitioned into Study 190-504, no change in ML score was observed over a maximum of 6 years of study follow-up. Of the other two patients who initiated treatment with a baseline ML score of 6, and aged under 3 years (but did not transition into Study 190-504), both patients remained at an ML score of 6 for the duration of available follow-up.<br>In the absence of data on how these patients would be expected to progress after 6 years, progression was assumed, although at a slower rate than for other patients. This assumption was based on feedback from clinical experts at two CLN2 centres in England. |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; HST, highly specialised technology; ML, motor language.

## B5. Priority question: The company assumed that initial stabilisers do not progress for the first 6 years of treatment with cerliponase alfa and justify this assumption based on what was observed in study 190-203 (<3 years old). The

**EAG notes that the follow-up of this study was 169 weeks (i.e., approximately 3.25 years). Please clarify the following:**

a) **How many patients treated with cerliponase remained on ML score 6 throughout the follow-up and what was the mean time on health state for these patients in the:**
    a. **'All patients' dataset;**
    b. **Study 190-203 full cohort.**

Table 72 presents the duration (years) of time with an ML score of 6 for patients who had a baseline ML score of 6. There were eight patients in the cerliponase alfa 'all patients' matched dataset who had a baseline ML score of 6, of which five came from the 190-203 cohort. All five patients in the cerliponase alfa Study 190-203 matched cohort that had a baseline ML score of 6 remained on ML score of 6 throughout the follow up. Therefore, the time in health state for the cerliponase alfa patients in the cerliponase alfa Study 190-203 cohort was equal to the duration of follow up.

Please note that:

- estimates for Study 190-203 do not include data following transition into Study 190-504; the two data sets are not currently linked, and so this analysis could not be completed within the required time frame.

- the comparison presented in Table 72 only includes patients in the 1:1 matched cohorts.

**Table 72: Time in ML 6 for patients who were baseline ML 6**

| Dataset | Treatment | n | Time in ML 6 (years); mean |
|---|---|---|---|
| 'All patients' matched dataset | Cerliponase alfa | 8 | 2.80 |
| | Natural history | 8 | 0.79 |
| Study 190-203 cohort matched dataset | Cerliponase alfa | 5 | 3.21 |
| | Natural history | 5 | 1.05 |

Abbreviation: ML, motor language.

b) **What was the rationale for assuming absence of progression over 6 years, given the follow-up in study 190-203?**

Of the Study 190-203 patients (aged less than 3 years) who initiated treatment with an ML score of 6 and transitioned into Study 190-504, no change in ML score was observed across

the two studies. Of the other two patients who initiated treatment with a baseline ML score of 6, and aged under 3 years (but did not transition into Study 190-504), both patients remained at an ML score of 6 for the duration of available follow-up.

Data for Study 190-203, completed in April 2022, is associated with 169 weeks (~3.25 years) of follow-up and Study 190-504, with data cut-off in April 2023, is associated with an additional 151 weeks (~2.90 years) of follow-up.

## *Adverse events*

**B6. The adverse events of treatment with cerliponase alfa included in the economic model were informed by study 190-202. Please justify why other sources of safety data were not considered and discuss the potential impact of using alternative data sources (e.g., 'all patients' in the pooled data used to inform transition probabilities, study 190-203, other studies reported on Section B.2.10 of the CS, etc.) on the cost-effectiveness model (ideally supported by scenario analyses).**

An overview of AE data for cerliponase alfa from all available studies was presented in Section B.2.10 of the company submission, and is reproduced in Table 73.

As a higher proportion of patients in Study 190-201/202 experienced AEs than for any other study, the use of AE data from Study 190-201/202 is expected to be conservative. The impact of this assumption is also expected to be negligible; extreme value scenarios in which AE rates are either doubled or set to zero result in a minimal change to the incremental cost-effectiveness ratio (ICER) (Table 74).

**Table 73: Safety overview**

| Study (Ref) | 190-201/202 (9) | 190-203 (1) | 190-501 (15) | 190-502 (16) | 190-504 (17) |
|---|---|---|---|---|---|
| **AE category** | **(N=24), n (%)** | **(N=14), n (%)** | **(N=37), n (%)** | **(N=27), n (%)** | **(N=48), n (%)** |
| Any AE | 24 (100.0%) | 14 (100.0%) | 24 (64.9%) | 25 (92.6%) | 21 (43.8%) |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 | 0 |
| AEs leading to dose interruption | 15 (62.5%) | 5 (35.7%) | 5 (13.5%) | 1 (3.7%) | 9 (18.8%) |
| AEs leading to study drug discontinuation | 0 | 0 | 0 | 0 | 1 (2.1%) |
| Any SAE | 21 (88%) | 12 (85.7%) | 17 (45.9%) | 15 (55.6%) | 16 (33.0%) |

| Study (Ref) | 190-201/202 (9) | 190-203 (1) | 190-501 (15) | 190-502 (16) | 190-504 (17) |
|---|---|---|---|---|---|
| **AE category** | **(N=24), n (%)** | **(N=14), n (%)** | **(N=37), n (%)** | **(N=27), n (%)** | **(N=48), n (%)** |
| SAEs leading to dose reduction | 12 (50%) | 0 | 0 | 0 | 0 |
| SAEs leading to dose interruption | NR | 2 (14.3%) | 4 (10.8%) | 0 | 7 (14.6%) |
| SAEs leading to study drug discontinuation | 0 | 0 | 0 | 0 | 1 (2.1%) |
| Any AE CTCAE Grade ≥3† | 21 (87.5%) | 10 (71.4%) | 14 (37.8%) | 8 (29.6%) | 12 (25.0%) |
| Death | 0 | 0 | 1 (2.7%) | 0 | 1 (2.1%) |
| Any treatment-related AE | 23 (96%) | 11 (78.6%) | 11 (29.7%) | 16 (59.3%) | 6 (12.5%) |
| Treatment-related SAEs | 8 (33%) | 7 (50.0%) | 2 (5.4%) | 6 (22.2%) | 1 (2.1%) |
| AESI‡ | | | | | |
| Status epilepticus | 2 (8.3%) | 1 (7.1%) | 1 (2.7%) | 4 (14.8%) | 2 (4.2%) |
| Hydrocephalus | 0 | 0 | 0 | 0 | 0 |
| Meningitis | 0 | 0 | 1 (2.7%) | 0 | 3 (6.3) |
| Hypersensitivity | 18 (75.0%) | 10 (71.4%) | 0 | 7 (25.9%) | 4 (8.3%) |
| TREs | 24 (100.0%) | 14 (100.0%) | 15 (40.5%) | 19 (70.4%) | 14 (29.2%) |
| Device-related events | 20 (83.0%) | 5 (37.5%) | 19 (51.4%) | 3 (11.1%) | 10 (20.8%) |
| Cardiovascular events | 7 (29.0%) | 3 (21.4%) | 0 | 3 (11.1%) | 0 |
| Unexpected rapid decline in CLN2 score | 0 | 0 | NR | 2 (7.4%) | NR |

Percentages were calculated using the total number of participants in the safety population (N for each treatment group) as the denominator. Participants with more than one AE of the same category were counted only once for that category.
†Relationship to the study drug and CTCAE grade was assessed by the investigator; ‡Prospective selection of AESI was based on non-clinical findings, known effects of other enzyme replacement therapies, and literature review of AEs associated with ICV delivery systems.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CLN2, neuronal ceroid lipofuscinosis type 2; CTCAE, common terminology criteria for adverse events; ECG, electrocardiogram; SAE, serious adverse event; TRE, temporally-related events.

**Table 74: Scenario analysis results – alternative AE rates**

| | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] |
| Scenario: AE rates doubled | [redacted] | 17.33 | [redacted] |
| Scenario: AE rates set to zero | [redacted] | 17.37 | [redacted] |

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

**B7. Priority question: The company does not include in the economic model adverse events related to the ICV device. Clinical advice to the EAG confirmed that, while events of device related infections were lower in clinical practice than on the cerliponase alfa clinical trial programme, patients treated with**

**cerliponase alfa would still be at risk of these adverse events with potential impacts on health-related quality of life and resource use due to the need to replace the device earlier and provide antibiotic treatment for up to 2 weeks. Please include a scenario analyses including the costs and disutility of adverse events of ICV related infections for patients treated with cerliponase, using available safety data sources.**

The proportion of patients who experienced ICV device-related infections was derived from clinical expert opinion, which suggested one device-related infection event per 800 infusions. The disutility of infection was derived from the published literature (26).

Antibiotics were selected based on the Study 190-202 CSR and insights from a CLN2 clinical centre. The antibiotics rifampicin, cephalosporin (ceftriaxone or cefotaxime), and linezolid were modelled for inclusion. In the absence of other data, an equal proportion of patients was assumed to receive rifampicin, cephalosporin (either one of ceftriaxone or cefotaxime), and linezolid. Antibiotic treatment regimens were derived from the British National Formulary (BNF) (Table 76). Costs were derived from the drugs and pharmaceutical electronic market information tool (eMIT) (Table 77) (27, 28).

A scenario analysis was conducted in which the cost and disutility associated with infection was included. This scenario is associated with a negligible change to the ICER (0.03%).

**Table 75: Disutility of ICV-related infections**

| | Value | Source |
|---|---|---|
| Proportion with ICV device-related infection | 0.125% | Clinical expert opinion. |
| Disutility | -0.20 | Song Y, Tai JH, Bartsch SM, Zimmerman RK, Muder RR, Lee BY. The potential economic value of a Staphylococcus aureus vaccine among hemodialysis patients. Vaccine. 2012;30(24):3675-82. |

Abbreviations: ICV, intracerebroventricular.

**Table 76: Antibiotics for ICV-related infections**

| | | Proportion receiving (%) | Administration | Dose, frequency | Duration (days) | Reference |
|---|---|---|---|---|---|---|
| Rifampicin | | 33.3% | Oral | 5 mg/kg, every 12 hours | 2 | BNF (28), rifampicin dose for prevention of secondary case of meningococcal meningitis |
| Cephalosporin | Ceftriaxone | 16.7% | IV | 90 mg/kg, once daily | 1† | BNF (28), ceftriaxone dose for bacterial meningitis and bacterial endocarditis, child 1 month – 11 years |
| | Cefotaxime | 16.7% | IV | 50 mg/kg, one dose | 1 | BNF (28), cefotaxime dose for treatment of suspected bacterial meningitis or meningococcal disease, child 1 month – 15 years |
| Linezolid | | 33.3% | Oral | 600 mg, every 12 hours | 10 | BNF (28), linezolid |

†Assumption, based on duration for cefotaxime.
Abbreviations: BNF, British National Formulary; ICV, intracerebroventricular; IV, intravenous.

**Table 77: Antibiotic cost of ICV-related infections**

| | | mg per unit | Units per pack | Cost per pack | Reference |
|---|---|---|---|---|---|
| Rifampicin | | 100 | 1 | £4.05 | eMIT (27) |
| Cephalosporin | Ceftriaxone | 1000 | 5 | £2.22 | |
| | Cefotaxime | 1000 | 10 | £6.05 | |
| Linezolid | | 600 | 10 | £5.79 | |

Abbreviations: eMIT, Drugs and pharmaceutical electronic market information tool.

**Table 78: Scenario analysis results – including ICV-related infections**

| | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] |
| Scenario: including ICV-related infection cost and disutility | [redacted] | 17.35 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

## *Mortality*

**B8. Priority question: The company has assumed that with the exception of patients in health state 9, patients are exposed only to the age and sex adjusted general population mortality. The company did not include neurodisability related mortality in the model (which was a NICE committee preferred assumption in HST12) due to no deaths being observed in the cerliponase alfa for health state trial programme in which neurodisability was the cause. The EAG has received clinical advice suggesting that disease related mortality is to be expected, particularly once the patient becomes bedbound (ML score 0) due to increased risk of pneumonia.**

a) **Please comment on the clinical plausibility of average life expectancy and proportion of patients still alive at the age of 88 years for patients treated with cerliponase alfa predicted by the economic model;**

In the economic model:

- The average life expectancy for cerliponase alfa patients is 56 years
- Approximately 10% of patients remain alive at 88 years of age.

It is currently unknown what long-term survival will look like for cerliponase alfa patients. However, cost-effectiveness remains relatively stable under alternative mortality

assumptions, as reduced survival also means reduced treatment costs. This effect is demonstrated in the scenario analysis presented in part b.

**b) Please provide scenario analysis including neurodisability mortality risk modelled as per HST12.**

BioMarin maintains that the impact of mortality due to neurodisability is negligible, given that no deaths pertaining to neurodisability have been observed in the cerliponase alfa trial programme (1, 29). However, to satisfy the request of the EAG, in line with HST12, neurodisability mortality risk ratios for each modelled health state and were derived from Cameron et al, 2007, a study of ten-year outcomes following traumatic brain injuries and are presented in Table 79 (30).

Inclusion of a neurodisability risk results in £1,776 (0.6%) reduction in the ICER (Table 80).

**Table 79: Neurodisability mortality risk ratio by health state**

| Health state | Risk ratio |
|---|---|
| 1 | 1.12 |
| 2 | 1.12 |
| 3 | 2.0 |
| 4 | 2.0 |
| 5 | 2.0 |
| 6 | 10.3 |
| 7 | 10.3 |
| 8 | 10.3 |
| 9 | 10.3 |

**Table 80: Scenario analysis results – including neurodisability mortality risk**

| | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] |
| Scenario: including neurodisability mortality risk | [redacted] | 17.31 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

**B9. Please consider reporting a scenario analysis including the mortality risk associated infections for patients with a ML score of zero. If evidence in CLN2 disease is not available to parameterise this scenario, evidence from diseases such as metachromatic leukodystrophies may be a useful proxy according to clinical advice to the EAG.**

Data to consider infection-related mortality due to being bedbound were derived from the published literature (Table 81)[1], and applied to all health states with an ML score of 0. In the absence of data in CLN2 for a paediatric population, the incidence of infection for patients with an ML score of zero was derived from a study exploring the pulmonary infection risk factors in long-term bedridden patients (31). A mortality risk ratio for patients with an infection and a ML score of zero was taken from the published literature in neonatal herpes simplex virus (HSV) infection, which reported a relative mortality risk of 3.6 in patients with HSV pneumonitis (32).

Results for the scenario including infection-related mortality for patients with ML score is presented in Table 82. The scenario results in a negligible change to the ICER.

**Table 81: Infection-related mortality data**

| | Value | Reference |
|---|---|---|
| Proportion of bed-bound patients with infection | 71.3% | Chen 2021 (31), proportion with pulmonary infection in patients with long bed rest. |
| Mortality risk ratio in patients with infection | 3.6 | Whitley 1991 (32), mortality relative risk of babies with HSV pneumonitis. |

Abbreviations: HSV, herpes simplex virus; ML, motor language.

**Table 82: Scenario analysis results – including infection-related mortality in ML score 0**

| | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] |
| Scenario: including infection-related mortality in ML score 0 | [redacted] | 17.35 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year.

## *Health related quality of life*

**B10. Please clarify how was general population age and sex adjusted utility estimated and what source informed this parameter.**

In line with current NICE guidance, general population utility values were taken from Hernandez-Alava et al, 2022 (33). Health state utility values from Gissen et al 2021 (34) are

[1] Mortality risk ratios for neurodisability and infection in health states associated with a ML score of 0 were assumed to be multiplicative when scenarios are considered jointly.

applied at the start of the model; for every subsequent year, a multiplier is applied based on the ratio between the general population utility values for current age and starting age.

### B11. Please provide a more comprehensive justification for the use of treatment-dependent utility values and indicate the reasons this approach was chosen instead of using treatment-independent utility values and applying disutilities associated with occurrence of the specific disease symptoms.

Treatment-dependent utility values were used in line with the estimates presented by Gissen et al (34), where differences in utility between cerliponase alfa and SoC patients were demonstrated, even when in the same model health state.

In addition to descriptions of motor and language, the vignettes used in the utility study included descriptions of:

- Tonic-clonic seizures
- Disease-related pain/distress
- Dystonia, myoclonus and spasticity
- Feeding tube use
- Social interactions
- Vision loss
- Ventilator use
- Incontinence
- Administration of cerliponase alfa.

Although it would be possible to model individual utility decrements for each of the included symptoms/disease manifestations, this approach would be associated with the following challenges:

- Utility decrements would need to be sourced in the appropriate paediatric population,
- Some vignette descriptions may not map easily to reported utility data – for example, “severe difficulty with social interactions”.

- It is unknown whether there may be overlap between the reported data, resulting in double counting.

The values presented by Gissen et al – in which all relevant aspects of CLN2 disease have been considered – were therefore used directly.

### B12. Priority question: Please provide a scenario analysis that applies EQ-5D-3L utilities derived from PedsQL™ data collected for patients in the 'all patients' pooled dataset.

The requested scenario analysis was not provided due to a comprehensive evaluation of several factors, as outlined below:

- All studies that collected PedsQL data also collected EQ-5D data directly.
    - Although EQ-5D data may not be sufficiently sensitive to capture all elements of CLN2 disease, this limitation is also expected to be present in data that have been mapped to EQ-5D.
    - Any differences between utilities based on the EQ-5D data and mapped PedsQL data are expected to be due to the limitations of mapping (i.e. that no mapping algorithm is able to predict perfectly), rather than differences in sensitivity.
- HRQoL data would not be available for either SoC patients or for the most severe health states; it would therefore be necessary to make assumptions similar to those made in the scenario analysis in which EQ-5D data from the MAA were used.
- Two mapping algorithms were identified in the HERC database of mapping studies (35): Khan et al (36) and Shafie et al (37).
    - The algorithm presented by Khan et al, was developed in children in the general population aged 11–15, and the algorithm presented by Shafie et al, was developed in patients with transfusion-dependent thalassemia.
    - As the algorithms were developed in relatively different patient populations, they may be less relevant for analysis of patients with CLN2 disease.

Considering these factors collectively, a scenario analysis involving the mapping of PedsQL data to EQ-5D was not considered informative.

**B13. Please provide scenario analysis applying the following:**

a. **Treatment-independent utility values, i.e., using the same utility values for Cerliponase alfa and standard of care (SoC) from Gissen et al. (vignette study), by taking an average across treatments;**

b. **The utility estimates from MAA to both Cerliponase alfa and SoC (i.e., treatment-independent values).**

A summary of the results of scenarios using treatment-independent utility values from the Gissen et al, 2021 vignette study and the MAA are presented in Table 83.

**Table 83: Scenario analysis results – treatment-independent utility values**

| | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] |
| a. Scenario: Gissen 2021, treatment-independent utility values | [redacted] | 16.88 | [redacted] |
| a. Scenario: MAA (all patients), treatment-independent utility values | [redacted] | 15.03 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; QALY, quality-adjusted life year.

**B14. Please provide detailed information about the study used to support assumptions on disutility among caregivers and siblings.**

a. **Please provide demographic details of the children with CLN2 disease (stage of disease progression and age) and;**

b. **Please provide demographic details of the siblings (age and, if available, the stage of disease progression of the sick sibling).**

The study “Challenges of living with and caring for a child affected by CLN2 disease” consisted of a focus group research day held in 2015 (38). The focus group was comprised of eleven caregivers, consisting of both current and bereaved caregivers, associated with six households and a total of eight children with CLN2 disease. The sex and age of the children with CLN2 disease are presented in Table 84.

**Table 84: Demographic details of children with CLN2 (Table 1, page 20, (38))**

| # | Household | Sex | Age (years) |
|---|---|---|---|
| 1 | 1 | Male | Deceased at age 11 |
| 2 | 1 | Female | NA |
| 3 | 2 | Female | Deceased at age 8 |

| # | Household | Sex | Age (years) |
|---|---|---|---|
| 4 | 3 | Female | 6 |
| 5 | 4 | Female | 6 |
| 6 | 4 | Male | 4 |
| 7 | 5 | Male | Deceased at age 5 |
| 8 | 6 | Female | Deceased at age 10 |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NA, not available.

Disease severity was collected using the Hamburg scale and completed by the caregivers of the four current patients with CLN2 disease, at the time of the study. Individual responses are not available, therefore mean results from the Hamburg scale are presented in Table 85.

**Table 85: Disease severity of children with CLN2 (n=4) (Table 5, page 23 (38))Table 86: Disease severity of children with CLN2 (n=4) (Table 5, page 23 (38))**

| | Mean (SD) |
|---|---|
| Walking ability | 0.25 (0.5) |
| Language function | 0.25 (0.5) |
| Visual function | 1.25 (1.5) |
| Frequency of seizures | 1 (1.15) |
| Total | 0.69 (1.01) |

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; SD, standard deviation.

Demographic details of the siblings of children with CLN2 disease are presented in Table 87. Data for the stage of progression of the sibling with CLN2 disease were not collected in the study.

**Table 87: Demographic details of the siblings of children with CLN2 (Table 3, page 22, (38))**

| Affected child | | Sibling | |
|---|---|---|---|
| **Sex** | **Age (years)** | **Sex** | **Age (years)** |
| Female | 6 | Male | 5 |
| | | Male | 3 |
| Female | Deceased at age 10 | Female | 11 |
| Female | Deceased at age 8 | Female | 12 |
| | | Female | 4 |
| Male | Deceased at age 5 | Female | 12 |
| Female | Deceased at age 10 | Female | 20 |
| Female | 9 | | |

Abbreviation: CLN2, neuronal ceroid lipofuscinosis type 2.

### B15. Please justify the linear increase in the disutility among caregivers and siblings with disease progression and detail the evidence used to data support this assumption.

In line with HST12, caregiver disutilities were informed by the study “Challenges of living with and caring for a child affected by CLN2 disease” (38). Caregivers of children with CLN2 (N=16) were asked to complete the EQ-5D-5L questionnaire and values were then cross-walked to 3L. The mean utility of the participating UK caregivers was compared with the age- and gender-matched general population utility value, reported using the EQ-5D-3L, derived from the Health Survey for England 2010 (38). The study identified the utility of caregivers was lower than that of their matched general-population controls (-0.108; $p<0.01$).

As data were not available for the stage of CLN2 disease progression of the children with CLN2 disease in the study, caregiver disutility for health states 1 and 2 were derived from Clinical expert opinion and a disutility of 0.108 was assumed to be representative of the caregivers of children with CLN2 disease in health states 6, the midpoint health state of the remaining health states (39). For the remaining states, it was assumed that disutility would increase linearly in the absence of data.

### B16. Please justify the assumption of a 50% reduction in caregiver/sibling disutility for the cerliponase alfa treatment compared to standard of care, indicating the evidence that supports the lower caregiver/sibling disutility with cerliponase alfa treatment and how the 50% value was selected.

For this reappraisal, caregiver disutilities from HST12 were validated in a series of advisory boards held with CLN2 disease clinical experts in 2023 (40). Experts expressed that cerliponase alfa-treated patients may experience a reduced need for seizure rescue medication, and that the amount of time watching and treating for seizures would be reduced accordingly. It may also be expected that the reduction in other progressive symptoms for patients would impact positively on both caregivers and siblings. Moreover, caregiver disutility may be lower for caregivers of patients with CLN2 disease who begin treatment earlier. Therefore, in the absence of other data, it was assumed that caregiver disutility for cerliponase alfa is 50% lower than for SoC.

### B17. In the economic model caregiver/sibling disability was applied for 30 years. Please justify the length of time during which caregiver/sibling disutility is applied and comment on how plausible it is that this disutility still applies

**for the proportion of patients in residential care who are 18 years and older from that age onwards.**

In line with the committee-preferred assumptions in HST12, caregiver and sibling disutility was assumed to apply for 30 years. This assumption is considered to be conservative as siblings may experience a lower quality of life over a longer life expectancy, as compared with people who do not have a sibling with CLN2 disease. Table 88 presents the results of a scenario analysis exploring removing this disutility for caregivers and siblings of patients with CLN2 disease who are in residential care.

**Table 88: Scenario analysis results – caregiver and sibling disutility duration**

| | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] |
| Scenario 1: Caregiver disutility not applied for patients in residential care | [redacted] | 17.37 | [redacted] |
| Scenario 2: Sibling disutility not applied to patients in residential care | [redacted] | 17.37 | [redacted] |
| Scenario 3: Neither caregiver nor sibling disutility applied to patients in residential care | [redacted] | 17.38 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; QALY, quality-adjusted life year.

## *Resource use and costs*

### B18. Priority question: The NICE scope specifies that the costs associated with diagnostic testing for CLN2 in people with CLN2 disease who would not otherwise have been tested should be included in the modelling. Clinical advice to the EAG suggests that testing is currently done for CLN2 disease because active treatment is available (i.e., cerliponase alfa). Please include a cost effectiveness scenarios analysis including the cost of CLN2 diagnose using enzyme activity testing of TPP1 protein.

Clinical advice provided to BioMarin confirmed that diagnostic testing for CLN2 disease would be undertaken irrespective of the availability of treatment and was conducted routinely prior to the availability of cerliponase alfa. Therefore, costs associated with testing are not expected to differ between the worlds in which cerliponase alfa is or is not reimbursed by NICE.

However, for completeness, an option has now been included in the cost-effectiveness model to select to include or exclude the costs of testing. Parameters used to inform this model option are presented in Table 89; in the absence of data for enzyme activity testing of

the TPP1 protein or the number of patients tested to identify one cerliponase alfa patient, assumptions based on clinical expert feedback have been used. However, functionality is available in the model to consider alternative values by overwriting current inputs.

The results of the exploratory scenario analysis in which testing is included are presented in Table 90; the impact of this assumption is expected to be associated with a negligible change to the ICER.

**Table 89: Parameters used to inform testing costs**

| Parameter | Value | Source |
|---|---|---|
| Cost per test | £100 | Assumption informed by clinical expert feedback. Note that this estimate includes the full enzyme panel, and so includes conditions other than TPP1 deficiency. |
| % of tested patients who are eligible for treatment with cerliponase alfa | 0.6% | Calculated as 4 positive cases in 700 tests. Clinical expert feedback estimated that approximately 700 tests for CLN2 disease are undertaken in the UK each year. The budget impact model submitted alongside this resubmission estimated that there are between 4 and 5 new cerliponase alfa patients each year. |

**Table 90: Scenario analysis results – including testing costs**

| | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] |
| Scenario: Include testing costs | [redacted] | 17.35 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

## *Cost-effectiveness results*

**B19. Priority question: The cost-effectiveness analysis results presented apply a commercial arrangement for cerliponase alfa that had not been approved by NHS England at the time of submission. Please provide all cost-effectiveness results in Sections B.3.9-10 (including Tables 86-89 and 91, Figures 19 -21) as well as in Appendix J (Tables 3 and 4) using the approved price for cerliponase alfa (i.e., list price, if the commercial arrangement proposed by the company is not yet approved at the time of submission for the points for clarification company response).**

The following results are presented in Appendix A, assuming list price for cerliponase alfa:

- Base-case results
- Probabilistic sensitivity analysis
- Deterministic sensitivity analysis
- Scenario analysis
- Disaggregated costs.

## *Probabilistic sensitivity analysis*

**B20. Priority question: The probabilistic sensitivity analysis currently appears to overwrite any changes to company's base-case parameter values with the default model parameters. This means that the economic model can only effectively be run probabilistically for the company's base case analysis and not for any other scenario. Please correct the VBA code, so it no longer resets default parameter values and allows to run any scenario analysis probabilistically.**

In order to run probabilistic sensitivity analysis for one scenario, the following steps can be taken:

1. Set up the relevant scenario on the model input sheets (e.g. by selecting from the dropdowns).
2. On the 'Control' sheet, either:
    a. Click on the button in cell C2 labelled 'Click to update default values with current values'; or
    b. Copy individual values from column C into column D; note that any parameters where the current value differs from the default value will be highlighted in red, and the text in cell B2 will state the number of parameters that are not at default.
3. Click on 'Click to run probabilistic sensitivity analysis' in B16 on the 'Sensitivity analysis' sheet.

In order to run multiple probabilistic scenario analyses:

1. Ensure that all relevant scenario analyses are set up on the ‘Control’ sheet

    a. From column AV onwards, new scenarios can be added by typing a scenario name in row 4, and entering the new value of the relevant parameter(s) in the rows below; for example, to set up a scenario with no discounting in column BS, type ‘No discounting’ in BS4 and enter 0 in cells BS5 and BS6

2. Select whether the scenario should be run deterministically only, or both deterministically and probabilistically in row 2 above the relevant scenario.

3. Click on ‘Click to run scenario analysis’ in cell B86 on the ‘Sensitivity analysis’ sheet

    a. The results of probabilistic scenarios will be presented in H109:K121.

## *Validation*

**B21. Priority question: The company presents a comparison of the observed 48-week rate of decline in ML score in Study 190-203 (and matched patients from Study 190-901) and the predicted corresponding estimates by the cost-effectiveness model (Table 1 (appendix J, CS). Please provide a similar comparison between trial outcomes and modelled results for:**

**a) The pooled ‘all patients’ dataset including matched patients in Study 190-901;**
**b) At further time points up to the end of available follow-up (e.g., 96 weeks, 169 weeks, etc.) for both:**
    **a. The pooled ‘all patients’ dataset including matched patients in Study 190-901;**
    **b. Study 190-203 including matched patients in Study 190-901**

Table 91 shows the ML score rate of decline for the trial outcome and predicted model outcome for the matched ‘all patients’ dataset and the matched 190-203 dataset at 48 weeks and every 48 weeks thereafter until the end of follow-up.

Predicted model outcomes for ‘all patients’ considers a starting age and distribution from the full population in Study 190-203, and transitions from the pooled ‘all patients’ data, and assumes no stabilisation.

Note that the ML score rate of decline from the trials assumes perfectly linear decline, and does not account for the impact of death (i.e., that patients with the lowest ML scores are expected to die sooner, increasing the average ML score in those who are alive); the latter is particularly relevant in the natural history data, where the risk of death is higher.

**Table 91: Comparison between trial outcomes and modelled results, ML score rate of decline**

| Dataset | Timepoint (weeks) | Outcome | Natural history | Cerliponase alfa |
|---|---|---|---|---|
| 'All patients' matched dataset | 48 | Trial outcome | 1.28 | 0.24 |
| | | Predicted model outcome | 1.73 | 0.38 |
| | 96 | Trial outcome | 2.57 | 0.49 |
| | | Predicted model outcome | 3.10 | 0.68 |
| | 144 | Trial outcome | 3.85 | 0.73 |
| | | Predicted model outcome | 3.92 | 0.92 |
| | 192 | Trial outcome | 5.13 | 0.97 |
| | | Predicted model outcome | 4.33 | 1.13 |
| | 240 | Trial outcome | 6.00 (max ML decline possible) | 1.22 |
| | | Predicted model outcome | 4.51 | 1.30 |
| | 288 | Trial outcome | 6.00 (max ML decline possible) | 1.46 |
| | | Predicted model outcome | 4.59 | 1.44 |
| | 336 | Trial outcome | 6.00 (max ML decline possible) | 1.71 |
| | | Predicted model outcome | 4.62 | 1.56 |
| | 384 | Trial outcome | 6.00 (max ML decline possible) | 1.95 |
| | | Predicted model outcome | 4.63 | 1.66 |
| | 432 | Trial outcome | 6.00 (max ML decline possible) | 2.19 |
| | | Predicted model outcome | 4.64 | 1.75 |
| Study 190-203 matched dataset | 48 | Trial outcome | 1.28 | 0.14 |
| | | Predicted model outcome | 1.66 | 0.21 |
| | 96 | Trial outcome | 2.55 | 0.28 |

| Dataset | Timepoint (weeks) | Outcome | Natural history | Cerliponase alfa |
|---|---|---|---|---|
| | | Predicted model outcome | 2.96 | 0.33 |
| | 144 | Trial outcome | 3.83 | 0.41 |
| | | Predicted model outcome | 3.76 | 0.40 |

Abbreviations: ML, motor language.

# Section C: Textual clarification and additional points

## *Search strategies*

**C1. The following search strategies are missing:**

- **Strategies for the DARE database; conference proceedings; health technology assessment sources; and clinical trial registries in Appendix D**
- **Strategies for conference proceedings; health technology assessment sources; and grey literature sources in Appendices G, H and I.**

**Please provide these, if available.**

The search strategy implemented in the original systematic literature review (SLR) for the Cochrane library as outlined in Table 6 of Appendix D covers searches for CDSR and CENTRAL as well as DARE. The search strategy in the following table for the 2024 SLR update only covers searches for CDSR and CENTRAL as DARE is only indexed up to March 2015 in Ovid.

Hand searching of conference proceeding was conducted for all SLR updates on the 26th September 2023. The following conferences were not formally hand searched as they are indexed in Embase: ISPOR and ISPOR Europe 2020, 2021, and 2022; WORLD Symposium 2020, 2021, 2022, and 2023. The following conferences were not hand searched due to lack of availability of abstracts: International Conference on Neuronal Ceroid Lipofuscinosis 2020/2021; and Society for the Study of Inborn Errors of Metabolism Meeting (SSIEM) 2020. The following conferences had not yet taken place at the time of hand searching: ISPOR 2023 and International Conference on Neuronal Ceroid Lipofuscinosis 2023.

Hand searching for ISPOR and ISPOR Europe conferences consisted of searching the following categories in each available poster session: “neurological disorders”, “drugs” and “rare and orphan diseases”. These categories were searched for clinical outcomes, economic evaluations, HTA, and RWE.

Hand searching for the Society for the Study of Inborn Errors of Metabolism Meeting (SSIEM) included the following keywords: “CLN2”, “Janky”, “Bielschowsky”, “LINCL”, “Ceroid”, “Lipofuscinosis”, “Batten”, “Amaurotic”, “Spielmeyer”, “Vogt”, “TPP”, and “tripeptidyl peptidase”.

The International Child Neurology Congresses were hand searched by viewing their Platform proceedings and ePoster proceedings.

Hand searching of health technology assessment (HTA) websites was conducted for all SLR updates on the 26th September 2023. The following HTA websites were hand searched: NICE, the Scottish Medicines Consortium (SMC), and the All Wales Medicines Strategy group (AWMSG). The following keywords were used: “CLN2”, “neuronal”, “Batten” and “NCL”. The keywords used in the hand searching of the HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA) were: “CLN2”, “neuronal”, “Batten”, and “cerliponase”.

Hand searching of clinical trial registries was conducted for the clinical SLR update on the 26th September 2023 via the United States National Institutes of Health (NIH) trial registry & results database and WHO ICTRP. The databases were searched using the advanced search functions and keywords consisted of “CLN2”, “NCL”, “cerliponase”, and “Batten”.

Hand searching of economic and utility repositories was conducted on the 27th September 2023 for the cost-effectiveness, HRQoL, and healthcare resource identification, measurement and valuation SLR updates. Hand searching of the Cost Effectiveness Analysis (CEA) Registry (https://cevr.tuftsmedicalcenter.org/databases/cea-registry); EQ-5D (https://euroqol.org/publications/search-for-eq-5d-documents/) and the University of Sheffield School of Health and Related Research Health Utilities Database (ScHARRHUD [https://www.scharrhud.org/]) consisted of the following keywords: “CLN2”, “neuronal”, “Batten”, and “cerliponase”. Hand searching of EconPapers within Research Papers in Economics (RePEc [https://econpapers.repec.org/]) consisted of the following keywords: “CLN2”, “neuronal AND ceroid”, “Batten” (in keywords and title), and “cerliponase”.

## C2. The EAG notes the following concerns with some search strategies:

### 1. Why, In Appendix D, were no dedicated HTA databases searched?

The original SLRs were conducted in 2018 and we do not have access to the supporting materials, therefore we cannot provide any further clarification on the SLR methodology or the omission of HTA database searches from the protocol. For the SLR updates undertaken to support the current submission, HTA websites were hand-searched as a supplementary measure in all SLRs and these included NICE, the SMC, the AWMSG and the HTA Database of the INAHTA.

2. **In Appendices G, H and I, the searches of NHS EED and HTA via the Cochrane Library databases on the Wiley platform have applied inappropriate limits.**

The searches of NHS EED and HTA databases were conducted as part of the SLRs undertaken to support HST12 and did not form part of the SLR updates conducted for this submission. As these SLRs were conducted in 2018, we regrettably do not have access to the supporting materials and therefore cannot provide any further clarification on the design or the search strategies and SLR methodology. Nevertheless, we do not anticipate that this should have any bearing on decision making with regards to the current submission.

3. **As NHS EED and HTA sources consist of economic evaluations and HTA evidence why did the company then filter results by technology assessments and economic evaluations?**

Please see response to question C2.2.

4. **For searches of NHS EED and HTA, there were 111 results at line 16 which were then reduced to 1 and 0 for NHS EED and HTA, respectively. Please can the company clarify whether any of the 111 results were relevant? The EAG has found relevant HTAs that were not included in the submission (e.g., the CADTH review of cerliponase alfa, https://www.cadth.ca/cerliponase-alfa).**

The CADTH review for cerliponase alfa was included in this submission, however data were only extracted for the cost-effectiveness SLR update (Appendix G) and the cost and healthcare resource identification, measurement and valuation SLR update (Appendix I). As the CADTH review did not present any health state utility values or clinical efficacy and safety data outside of that which had been presented in Document B2 of the submission, it was ineligible for inclusion in the health-related quality of life (Appendix H) and clinical SLR (Appendix D) updates.

**C3. For all searches the PRISMA diagrams are unclear and appear to contain errors. Please could these be checked and corrected. The EAG notes the following issues:**

1. **In Appendix D, Figure 1:**
    a. **'congress' is vague and other conference proceedings are not listed;**
    b. **the searches of clinicaltrials.gov and HTA sources are not listed;**
    c. **there are searches of the EMA listed but these do not appear in the sources searched; and WHO ICTRP appears twice.**

Appendix D, Figure 1 pertains to the original SLR that was conducted in 2018 to support HST12. Regrettably, we do not have access to the supporting documents of this submission, and therefore cannot provide any further clarification on the SLR methodology.

2. **In Appendices G, H and I, Figure 1:**
    a. **EconLit wrongly lists 0 results instead of 1;**
    b. **'congress' is vague and other conference proceedings are not listed; RePEc and INAHTA are not listed;**
    c. **Some sources listed under 'supplementary database searches' are not databases.**

Figure 1 in appendices G, H, and I pertain to the original SLRs that were conducted in 2018 to support HST12. Regrettably, we do not have access to the supporting documents of this submission, and therefore cannot provide any further clarification on the SLR methodology.

3. **In Appendix H, Figure 2, the PRISMA for the update searches does not match the hits obtained by the search strategies.**

We have examined the search strategies for the January 2024 SLR update outlined in Sections H.1.2.1.2 for Embase, H.1.2.2.2 for Medline and H.1.2.4 for EconLit. These search strategies show that the final number of hits were 132, 92, and 1, respectively, which align with the numbers presented in Figure 2.

**C4. In Appendix D, there are no search terms for real world evidence, even though this is part of the criteria. Please clarify whether real world evidence was searched for.**

To ensure that the SLRs remained reproducible and systematic, the search strategies implemented in the SLR updates for this submission are the same as those used in the original SLRs undertaken to support HST12. Note that no amendments were made, with the

exception of the addition of date limits. The search strategies for the clinical SLR includes filter for observational studies which is intended to capture studies presenting real world evidence. The filter feature MESH and free text terms including, but not limited to, " exp Cohort Studies/ or exp Cohort study/", "Longitudinal$.tw."and "(case stud$ or case report$).ti."

## *Model file and references*

### C5. In the model, the values of cost data worksheet cell D50, D53, D64 are different from the CS, Table 67, p158. Please identify which ones are correct and provide the updated submission.

The cost values are incorrect in the company submission dossier only. An updated version of Table 67 (pg 158) of the company submission is presented in Table 92; corrected values are denoted in ***bold and italics***. Please note, this correction results in no change to the base-case results presented in the original company submission.

**Table 92: Health state resource use costs**

| | Unit cost | | Reference | |
|---|---|---|---|---|
| | First attendance | Subsequent attendance | First attendance | Subsequent attendance |
| Specialist clinician† | £439.81 | ***£203.93*** | NHS reference costs, 2021–22, WF01B, Non-Admitted Face-to-Face Attendance, First, Consultant-led, Paediatric Neuro-Disability (41) | NHS reference costs, 2021–22, WF01B, Non-Admitted Non-Face-to-Face Attendance, Follow-up, Consultant-led, Paediatric Neuro-Disability (41) |
| Specialist nurse‡ | £109.98 | £109.98 | NHS reference costs, 2021-22, N29CF, Other Specialist Nursing, Child, Face to face (41) | – |
| General practitioner | £41.00 | £41.00 | PSSRU 2022. Unit costs for a general practitioner, per surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualification costs (41) | – |
| Community paediatrician | £487.09 | ***£334.64*** | NHS reference costs, 2021-22, WF01B, Non-Admitted Face-to-Face Attendance, First, Consultant-led, Community Paediatric Service (41) | NHS reference costs, 2021-22, WF01B, Non-Admitted Non-Face-to-Face Attendance, Follow-up, Consultant-led, Community Paediatric Service (41) |
| Speech/language therapists | £143.21 | £143.21 | NHS reference costs, 2021-22, A13C1, Speech and Language Therapist, Child, One to One (41) | – |
| Physiotherapist | £132.15 | £132.15 | NHS reference costs, 2021-22, A08C1,Physiotherapist, Child, One to One (41) | – |
| Family support worker | £33.88 | £33.88 | PSSRU 2018. Family support worker, unit cost per hour. £31 inflated from 2018 prices to 2022 prices (41) | – |
| Ophthalmologist | £161.06 | ***£119.31*** | NHS reference costs, 2021-22, WF01B, Non-Admitted Face-to-Face Attendance, First, Consultant-led, Paediatric Ophthalmology (41) | NHS reference costs, 2021-22, WF01B, Non-Admitted Non-Face-to-Face Attendance, Follow-up, Consultant-led, Paediatric Ophthalmology (41) |
| Health visitor | £94.25 | £94.25 | NHS reference costs, 2021-22, N03F, Health Visitor, Other Clinical Intervention (41) | – |
| Occupational therapist | £167.91 | £167.91 | NHS reference costs, 2021-22, A06C1, Occupational Therapist, Child, One to One (41) | – |
| Caregiver costs | £38,453.33 | £38,453.33 | NHS. Agenda for change – pay rates. Average of salaries for a band 6 nurse (<2 years' experience: £35,392; 2-5 years' experience: £37,350; 5+ years' experience: £42,618) (42) | – |

| | Unit cost | | Reference | |
|---|---|---|---|---|
| | First attendance | Subsequent attendance | First attendance | Subsequent attendance |
| Critical care bed days | £7,251.91 | £7,251.91 | NHS reference costs, 2021-22, XB01Z, Paediatric Critical Care, Advanced Critical Care 5 (Paediatric Intensive Care Unit) (41) | – |
| Hospitalisation costs | £3,702.95 | £3,702.95 | NHS reference costs, 2021-22, XB02Z, Paediatric Critical Care, Advanced Critical Care 4 (Paediatric Intensive Care Unit) (41) | – |
| Palliative care | £167.30 | £167.30 | NHS reference costs, 2021-22, N21CF, Specialist Nursing, Palliative/Respite Care, Child, Face to face (41) | – |
| Educational support | £1,643.31 | £1,643.31 | PSSRU 2017. Education support, children aged 4-11 with low functioning autism living in private households with family. £1,485 inflated from 2017 prices to 2022 prices (43) | – |
| Cardiologist | £169.39 | £169.39 | NHS reference costs, 2021-22, Total outpatient attendances, service code 320, Cardiology Service (41) | – |

†Includes: neurologists, respiratory consultants, etc.; ‡Includes epilepsy nurse, nurse specialist, community nurse, etc.
Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

**C6. Priority question: Please provide access to the reference 33: ICON. Challenges of living with and caring for a child affected by CLN2 disease, a type of Batten disease - Focus Groups and Home Surveys - Final Report. Data on File. 2016.**

The reference has been included in the provided updated reference pack and is named “ICON Report (Data on File)”.

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# Appendix A - Base-case results, cerliponase alfa list price

## Base-case incremental cost-effectiveness analysis results

Base-case results for cerliponase alfa vs SoC are presented in Table 93 and Table 94.

**Table 93: Base-case results (deterministic) – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | 5.37 | –0.28 | – | – | – | – | – |
| Cerliponase alfa | [redacted] | 22.78 | 17.07 | [redacted] | 17.41 | 17.35 | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 94: Net health benefit – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | NHB at £300,000 |
|---|---|---|---|---|---|
| SoC | [redacted] | –0.28 | – | – | – |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; SoC, standard of care.

## Probabilistic sensitivity analysis

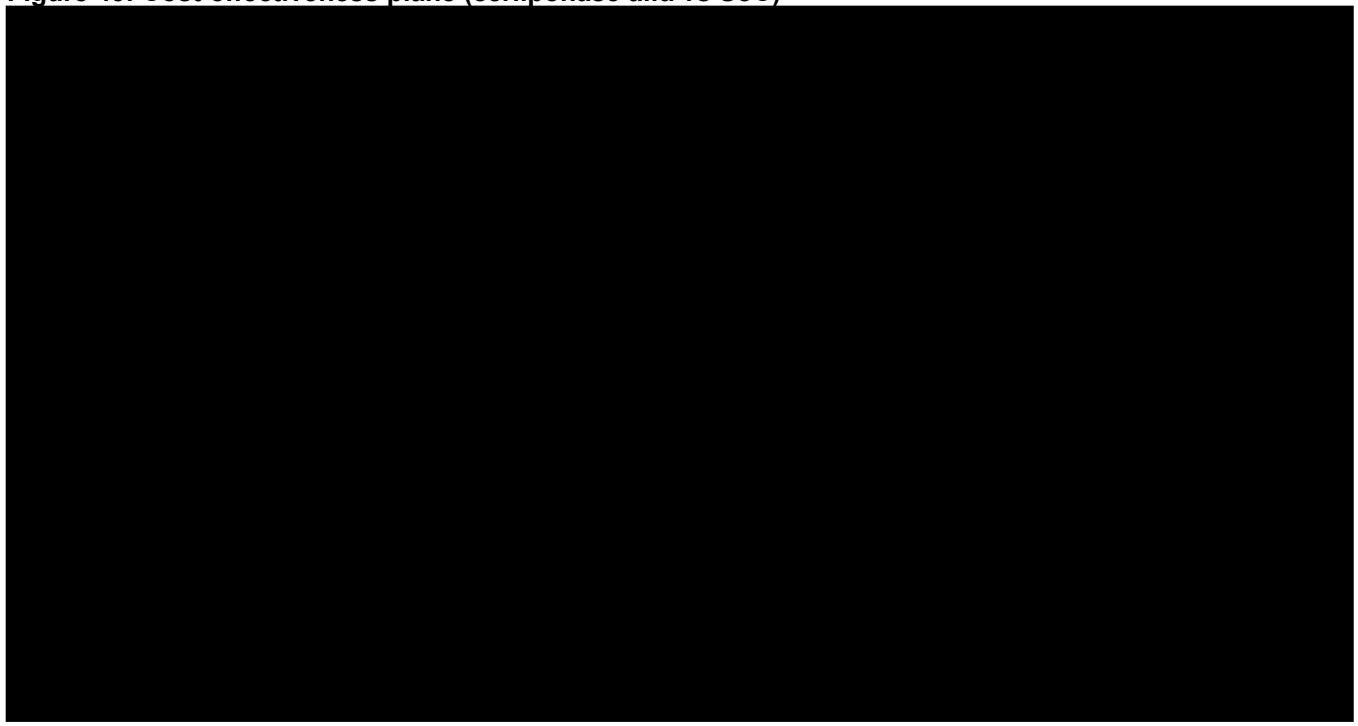
Results of probabilistic sensitivity analysis (PSA) of cerliponase alfa, at list price, versus SoC are presented in Table 95. The cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC) are presented in Figure 43 and Figure 44 respectively.

**Table 95: Probabilistic sensitivity analysis results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| SoC | [redacted] | –0.14 | – | – | – |
| Cerliponase alfa | [redacted] | 17.50 | [redacted] | 17.64 | [redacted] |

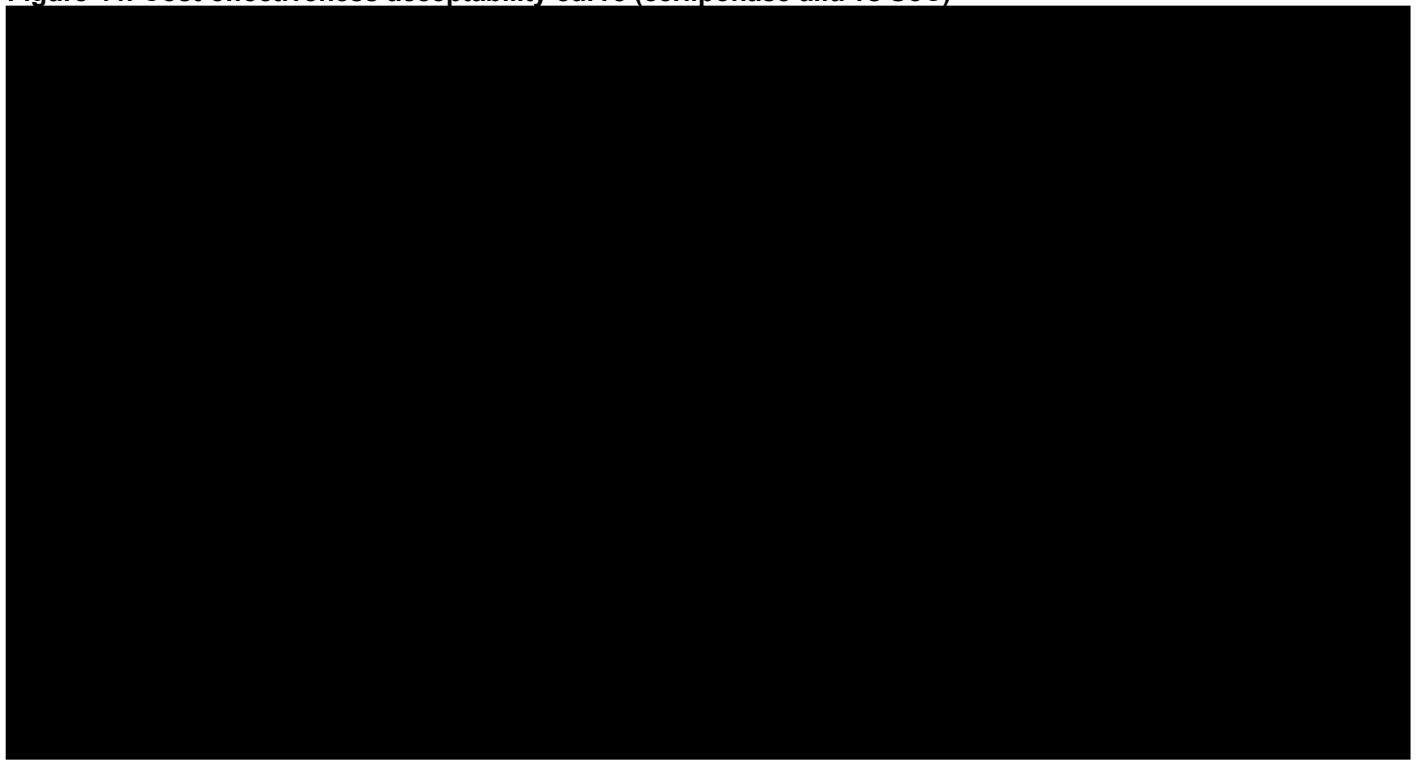
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Figure 43: Cost-effectiveness plane (cerliponase alfa vs SoC)**



Abbreviations: QALYs, quality-adjusted life years; SoC, standard of care.

**Figure 44: Cost-effectiveness acceptability curve (cerliponase alfa vs SoC)**



Abbreviations: SoC, standard of care.

## Deterministic sensitivity analysis

The results of deterministic sensitivity analysis of cerliponase alfa, at list price, versus SoC are presented in Table 96, and a tornado diagram of deterministic results is presented in Figure 45.

**Table 96: Deterministic sensitivity analysis results**

| Parameter | ICER at lower value of parameter | ICER at upper value of parameter |
|---|---|---|
| Transition intensity, cerliponase alfa, Study 190-203, 1 to 2 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 5 to 6 | [redacted] | [redacted] |
| Vision loss utility multiplier | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 2 to 1 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 2 to 3 | [redacted] | [redacted] |
| Transition intensity, SoC, Study 190-203, 1 to 2 | [redacted] | [redacted] |
| Transition intensity, SoC, Study 190-203, 2 to 3 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, Study 190-203, 3 to 2 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, all patients, 6 to 7 | [redacted] | [redacted] |
| Transition intensity, cerliponase alfa, all patients, 6 to 5 | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio.

**Figure 45: Tornado diagram**



Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care.

## Scenario analysis

Scenario analyses considering the list price of cerliponase alfa were performed, in line with scenarios presented in the original company submission Section B.3.10.3. Results of scenario analysis at list price are presented in Table 97.

**Table 97: Scenario analysis results (cerliponase alfa list price)**

| Scenario | Incremental costs | Incremental QALYs | ICER (£/QALY) | % change from base case ICER |
|---|---|---|---|---|
| Base case | [redacted] | 17.35 | [redacted] | [redacted] |
| Treatment discontinuation at health state 7 (ML score 0) | [redacted] | 17.79 | [redacted] | [redacted] |
| No treatment discontinuation | [redacted] | 17.86 | [redacted] | [redacted] |
| Starting distribution: Study 190-203 | [redacted] | 11.78 | [redacted] | [redacted] |
| Starting distribution: MAA (new patients) | [redacted] | 7.82 | [redacted] | [redacted] |
| Source of transitions: All patients | [redacted] | 14.27 | [redacted] | [redacted] |
| Source of transitions: All patients (piecewise at 6 months) | [redacted] | 22.86 | [redacted] | [redacted] |
| Duration of ML 6 stabilisation: 12 years | [redacted] | 18.52 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 75% | [redacted] | 19.54 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 100% | [redacted] | 22.11 | [redacted] | [redacted] |
| Source of utility values: MAA | [redacted] | 16.88 | [redacted] | [redacted] |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

## Disaggregated costs

**Table 98: Summary of predicted resource use by category of cost**

| Health state | Cost cerliponase alfa | Cost SoC | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Treatment costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Infusion costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 1 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 2 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 3 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 4 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 5 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 6 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Health state | Cost cerliponase alfa | Cost SoC | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Health state 7 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 8 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Health state 9 costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Adverse event costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Distress costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Dystonia costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Myoclonus costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Feeding tube replacement cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Seizure costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Epilepsy medication cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Vision loss costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Residential care costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: SoC, standard of care.

NICE National Institute for Health and Care Excellence

# Highly Specialised Technology

# Guidance review following a period of managed access - Patient organisation submission

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

**PLEASE NOTE:** You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

## Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

## This form has 8 sections

Section 1 - About you

Section 2 - Living with the condition and current treatment in the NHS

Section 3 - Experience, advantages and disadvantages of the treatment during the Managed Access Agreement [MAA]

Section 4 - Patient views on assessments used during the Managed Access Agreement (MAA)

Section 5 - Patient population (including experience during the Managed Access Agreement (MAA)

Section 6 - Equality

Section 7 - Other issues

Section 8 - Key messages – a brief summary of the 5 most important points from your submission

NICE National Institute for Health and Care Excellence

# Section 1. About you

### Table 1 Name, job, organisation

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | Batten Disease Family Association (BDFA) |
| **3. Job title or position** | [redacted] |
| **4a. Provide a brief description of the organisation. How many members does it have?** | The BDFA was formed in 1998 and is the only patient organisation in the UK that aims to support families, raise awareness, and facilitate research into the group of devastating neurodegenerative disorders commonly known as Batten disease. We support a very small community of 125 diagnosed children with various forms of Batten disease. Almost half of all children diagnosed with any form of Batten disease in the UK have CLN2.<br><br>The BDFA objectives are to:<br>• Preserve and protect the health and promote the welfare of persons affected by all types of Batten disease.<br>• To provide support and advocacy for affected families through a holistic support service, including access to a family wellbeing/counselling service, a peer befriending programme and facilitating a community for families to connect with one another.<br>• To advance the education of the medical profession and the general public on the subject of Batten disease and its implications for the family.<br>• To promote research into the management of Batten disease and to publish the useful results thereof and to support organisations prompting research into Batten disease.<br><br>We are members of The UK LSD Patient Collaborative Group, Newborn Screening Collaborative, the Specialist Healthcare Alliance, the Genetic Alliance Rare Disease Action Plan Patient Advisory Group and Patient Empowerment group. The BDFA also has membership for the Disabled Children's Partnership, Together for Short Lives and Eurodis. |

| | |
|---|---|
| **4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]**<br>**If so, please state the name of company, amount, and purpose of funding.** | BioMarin grants to the BDFA March 2023<br>- Patient Travel Support for treatment -£10,000<br>- BDFA-led Research Study - £10,000<br>- Regional work supporting the development of new treatment centres across the UK - £4,000<br>- BDFA Conference, later redirected to family support services due to conference being cancelled - £15,000. |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | Information for this submission has been gathered by the following means:<br>• Results from a National survey with families of children diagnosed with CLN2 run by the BDFA. Thirty-one parent/carers participated in the survey providing information about 31 children treated with Cerliponase alfa.<br>• Results from a National survey with educational workers from schools attended by children diagnosed with CLN2. Thirteen teachers participated in the survey providing information about 14 children treated with Cerliponase alfa.<br>• The results of a UK published study on the impact of COVID-19 pandemic on families and children with CLN2 (Mortensen et al, 2022 (available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8767529/, [accessed 10.10.2023])).<br>• Regular communication with the CLN2 Community.<br>• Regular contacts with the Scientific Committee set up by the BDFA which is made of leading UK clinical experts in Batten disease. |

# Section 2 Living with neuronal ceroid lipofuscinosis type 2 (CLN2) and current treatment

**Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment.**

| | |
|---|---|
| **6. What is it like to live with CLN2?**<br>Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life).<br>For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings? | The diagnosis of Batten disease is a cruel and devasting blow to a family who has already been on a lengthy diagnostic journey only to discover their precious child has a progressive, terminal disease that has no cure, few treatment options and a genetic component that may affect their other children.<br><br>The average age of a child at diagnosis is 4 years (52%) (parent survey Q8) with only 17% of children diagnosed at less than 3 years old. Initially children with CLN2 Batten disease appear to develop normally for the first 18 months – 2 years of life with the average age of noticing symptoms being 3 years (56%) (parent survey Q12), although some families noticed something wasn't right earlier (less than 3 years – 40% and less than 2 years – 16%). The most frequent first symptoms were language issues (36%) and seizures (39%) (parent survey Q13), both of which are relatively common in children (1 in 200 children are diagnosed with epilepsy and 1 in 5 with delayed speech). These account for 75% of first symptoms. As these symptoms are not specific to Batten disease, there is a delay in diagnosis with less than 42% receiving a diagnosis within a year and 25% taking more than 2 years (parent survey Q15). During this time parents become more worried, seeing on average approximately 4 specialists from different disciplines, but some saw as many as 10, all while their child manifests more symptoms (parent survey Q15-21). Almost 2/3rds of parents asked felt that this, in conjunction with lengthy waiting times, contributed to a delay in diagnosis.<br><br>• *"An initial diagnosis of dyspraxia stopped any further attempts to diagnose for around 2 years, until symptoms worsened."*<br><br>• *"No one believed me as mother."*<br><br>CLN2 Batten disease affects every aspect of a child's development and day-to-day living and brings multiple challenges to families of affected children. Seventy-four percent of parents who participated in the survey stated that they needed financial support, home adaptations and time off work (parent survey Q87-104, p48-55). Parents also require social care, mental health support and personal assistance to be able to cope with daily tasks of caring for their child: |

- *"Largely, we have been very well and urgently supported. Adaptations to our home was probably the most frustrating service due to initial poor management and illogical processes. Yet we have been thankful for the outcomes."*

- *"Took around a year to get XXX into a specialist school due to lack of funding."*

CLN2 has a negative impact on the affected children (parent survey, Q126-134, p69-73) such as self-care (dressing, dental hygiene), ability to play games, ability to play with friends, participate in family activities and their schooling:

- *"XXX has a movement disorder which effects the movement in his hands so is unable to do a lot when it comes to joining in games and playing, he is also in a wheelchair so needs 24-hour care which impacts certain things he can join in with."*

Surveyed teachers stated that CLN2 negatively impacted the ability of all affected children to learn new skills, playing with friends, eating, and drinking. Ninety-two percent of teachers reported that children had fatigue, visual impairment, had to use a wheelchair, and were unable to use the toilet independently, whilst 77% of teachers stated that affected children could not feed independently, were using a speech therapist during school time and were unable to attend after-school clubs (education survey Q19-48).

Caring for children with CLN2 has a profound negative impact on unaffected siblings (family survey, Q173-189) such as their physical health (mostly due to lack of sleep and time, feeding and physical carrying), mental health (mostly due to uncertainty, anxiety, feeling of guilt, lack of personal time and schooling), education, activities with friends and family life:

- *"We have three children who do not have Batten Disease. Having a sibling with this disease affects each of our three children differently. Our oldest (16) really struggles, he has witnessed a lot before diagnosis which he can remember for example uncontrollable seizures. He also understands the importance of remaining on treatment and what will happen if the treatment is removed. He is a very sensitive person who worries a lot. Our middle child (15) is not affected at all, he takes everything as it comes, and it is not in his nature to worry. Our youngest (3) is too young to understand."*

- *XXX's sibling has learned to help and do caring for XXX. Anxiety has crept into XXX's sibling's life - however the school have really helped work this through with him. It affects his ability to*

| | |
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| | *concentrate, and he now has outbursts of rage and emotion. Even if emotion is due to an unrelated situation - it will then trigger sadness about XXX."* |
| **7. What do carers experience when caring for someone with the condition?** | CLN2 Batten disease affected children need extensive care from their parents and wider family (family survey Q148-172). Eighty-four percent of surveyed parents are full-time carers and reported that caring for their child/children had a significant negative impact on their physical health (mostly due to physical lifting, lack of sleep and lack of personal time), mental health (mostly due to uncertainties, anxiety and depression), their social well-being, working life and professional career (39% no longer in employment and 26% working reduced hours) and family finances:<br><br>• *"A lot less finances to be able to "do" things both with family and friends. Likewise sleep deprivation means we are knackered at night, and we are unable to pay for night carers. Likewise, council won't pay for night carers until it is end of life care. We have gained experience and knowledge that we wouldn't have had and are able to pass this onto other newly diagnosed families. It's a VERY intense education. Likewise, now being unemployed means we are becoming less "employable" to future companies due ageing working knowledge."*<br><br>• *"I find the mental load of being a CLN2 parent so all-consuming that it can be tricky to think about much else."*<br><br>Parents strive to do their best for their children and retain normal family activities but found it difficult to travel due to needing to take more items, the increased costs and flying to a new time zone risks disorientation creating a stressful experience.<br><br>The children need the use of regular services to maintain their quality of life which takes time to arrange in the first place and then to access at regular intervals. Getting services can be difficult.<br><br>• *"At the start of this journey in 2015 it was very hard to get these services in place due to our son being very well at the time of diagnosis. Professionals did not believe he needed additional services whereas we believed these should be in place for as and when he needed them. As our son was diagnosed before a treatment was available his symptoms appeared very quickly, and we would often find that by the time he made his way to the front of a waiting list for a piece of equipment his skills would have changed, and he would no longer be in need of that piece of equipment but* |

| | |
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| | *instead would need something different. He would then be added to another waiting list and the cycle continued."*<br><br>The genetic component of diagnosis can affect the decision to have more children. While some parents told us that their families were completed before receiving the diagnosis, others were open to the use of IVF and PGT to avoid having another affected child although this route also has difficulties.<br><br>• *"After learning my daughter was diagnosed with CLN2 I was very hesitant on having any kids in the future. My decision has since changed after speaking with relevant genetic support professionals."*<br><br>• *"Because we had a neuro-typical child first, we would have to pay for private IVF/sperm washing which is just too expensive; and we couldn't go through the emotional rollercoaster of conceiving naturally and then terminating the child."* |
| **8. What do patients and carers think of current treatments and care available on the NHS?**<br>Please state how they help and what the limitations are. | Currently there is no cure for CLN2 disease, and the treatments are largely supportive. Due to high symptom load and rapid decline, the management is complex requiring multidisciplinary medical and social care to maintain a good quality of life for the children and their families. Generally, supportive treatments (e.g., pharmacological management of seizures but complete control is not always achieved, movement disorder and pain, speech and language therapy, physiotherapy and occupational therapy, family and palliative care, supporting with feeding and managing sleep disturbances) are available as per the CLN2 Management Guidelines (Mole S et al, 2021, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8059011/ [accessed 04.12.2023]).<br><br>However, as recorded in the survey responses, there is a lack of defined patient pathways for patients with CLN2 and other types of Batten disease resulting in deficiencies in general care provision such as social care and education and uncoordinated supporting services, causing anxiety and having a negative impact on quality of life of affected families. |
| **9. Considering all treatments available to patients are there any unmet needs for patients with this condition?**<br>If yes please state what these are. | Delay to diagnosis (please refer to our evidence submission in Section 4, point 14 and Section 5, point 18).<br><br>Families of affected children consider a cure or an effective treatment that prolongs life with a good quality of life as an important unmet need. Although symptomatic treatments help to manage the symptoms, they do not address the underlying cause, a lack of the enzyme TPP1. Uninterrupted access to Cerliponase alfa is therefore essential to preserve skills and stop/delay progression of the disease: |

| | |
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| | • *"I am always hoping for a cure but in the absence of that, a treatment which helps my child live well," and "To benefit my child's health and happiness."*<br><br>Treatment to prevent or slow down the progression of vision loss. |

# Section 3 Experience during the managed access agreement (MAA)

### Table 3 Experience, advantages and disadvantages during the MAA

| | |
|---|---|
| **10. What are patients' and carers' experience of accessing and having the treatment?**<br>• Please refer to the MAA re-evaluation patient submission guide | Over 70% of parents stated that their children required the ongoing use of a physiotherapist, occupation therapist, dietician, and speech therapist (family survey Q87-90).<br><br>Cerliponase alfa is currently only accessible in a hospital setting. Eighty-four percent of families travelled to hospital by car and had access to treatment within a 2-hour journey time. Only 7% of families required an overnight stay after infusion but if the start time was delayed it affected the journey time home (family survey Q42-48). Now there are other sites throughout the country closer to patients and families which made significant improvement to the lives of the family:<br><br>• *"Opening the centre in Manchester has massively improved our lives. Previously we travelled from Leeds to London. An overnight stay was always required. Now, we can be there and back in the same day with minimal disruption to family/home life."*<br><br>Families reported broad-ranging impacts of the COVID-19 pandemic on the care of their children. Some families reported anxiety about obtaining medicines, delays to prescriptions for standard medicines, being challenged about the frequency of prescriptions, and unexpected changes to formulations of some medicines. One family with a newly diagnosed child were unable to meet their paediatrician face to face. Others reported delays in specialist appointments (cardiac studies, sleep studies, urology) and one commented on the inadequacy of an ophthalmology assessment done by telephone (Mortensen A et al. (2022 (available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8767529/, [accessed 10.10.2023])). |

| | |
|---|---|
| | The families interviewed in the current study were clearly determined to continue Cerliponase alfa treatment during restrictions, despite extreme anxiety about travelling and attending hospital, as they considered that the benefits of the treatment outweighed the potential risk.<br><br>• *"We would therefore get up at 2am to start the 5-hour drive to London for treatment. We would spend the whole day in hospital before making the 5-hour drive home. It was extremely tiring but something we never once questions ourselves doing as our children needed treatment and we were just so grateful that even during a global pandemic we were able to continue with the treatment our children needed to stay alive and healthy."* |
| **11. What do patients and carers think are the advantages of the treatment?**<br>Please refer to the MAA re-evaluation patient submission guide | Parents participating in our survey were asked whether there were improvements, stabilisation, or deterioration of several symptoms associated with the disease.<br><br>Eighty-four percent of parents stated that their children experienced substantial improvement or stabilisation in seizure severity, frequency and duration (family survey Q51-52).<br><br>• *"For our son, seizures have improved massively, going from many daily tonic clonic seizures to one maybe two tonic clonic seizure per year."*<br><br>The surveyed teachers also noticed that seizures were being positively impacted by the treatment with Cerliponase alfa:<br><br>• *"Seizure activity is almost daily in school; however, their duration and occurrence are slightly reduced when they return to school after infusion."*<br><br>The majority of parents also reported improvement or stabilisation in relation to clumsiness, coordination, balance and movement, dystonia, myoclonus, limb weakness, ability to speak, mood and behaviour, sleep, pain and tiredness and fatigue (family survey Q55-68):<br><br>• *She is very mobile, sleeps great, never noticed any pain etc only thing is we've not noticed any change in vision."* |

| | |
|---|---|
| | • *"Seizures are well controlled, Mobility and swallowing slightly deteriorated in the first year as expected then stabilized, sleep is remarkably better, myoclonus is lot better, fatigue and tiredness is little better, some of that is due to the antiepileptics".*<br><br>• *"I've noticed major improvements since starting with the treatment, he's got so much better with everything, and we have not noticed any deterioration".*<br><br>Ninety-seven percent of parents considered the benefit of treatment with Cerliponase alfa as very important in relation to stabilisation of disease, activities of daily living, quality of life and leisure time (family survey Q69-74):<br><br>• *"Life expectancy for children with CNL2 Batten Disease is just 6-12 years. Our son will turn 13 in a couple of months. He still has a fantastic quality of life, because of this treatment he is still able to do many things that he enjoys in life including swimming and going aboard on holiday with his family. He is still able to show his emotions and can tell us through facial expressions when he is happy or sad. He smiles and laughs… especially if someone is doing something they are not supposed to which shows his understanding of the world around him."*<br><br>• *"The treatment has really stabilised his condition and he is thriving, very happy and enjoying an excellent quality of life."*<br><br>• *"Without the medication, XXX would have deteriorated so much more and at much higher rate. Therefore, Brineura is unparalleled in terms of importance in our lives, and we'd move heaven and earth to attend treatments. It gives us time, quality of life, and skills for a longer time."* |

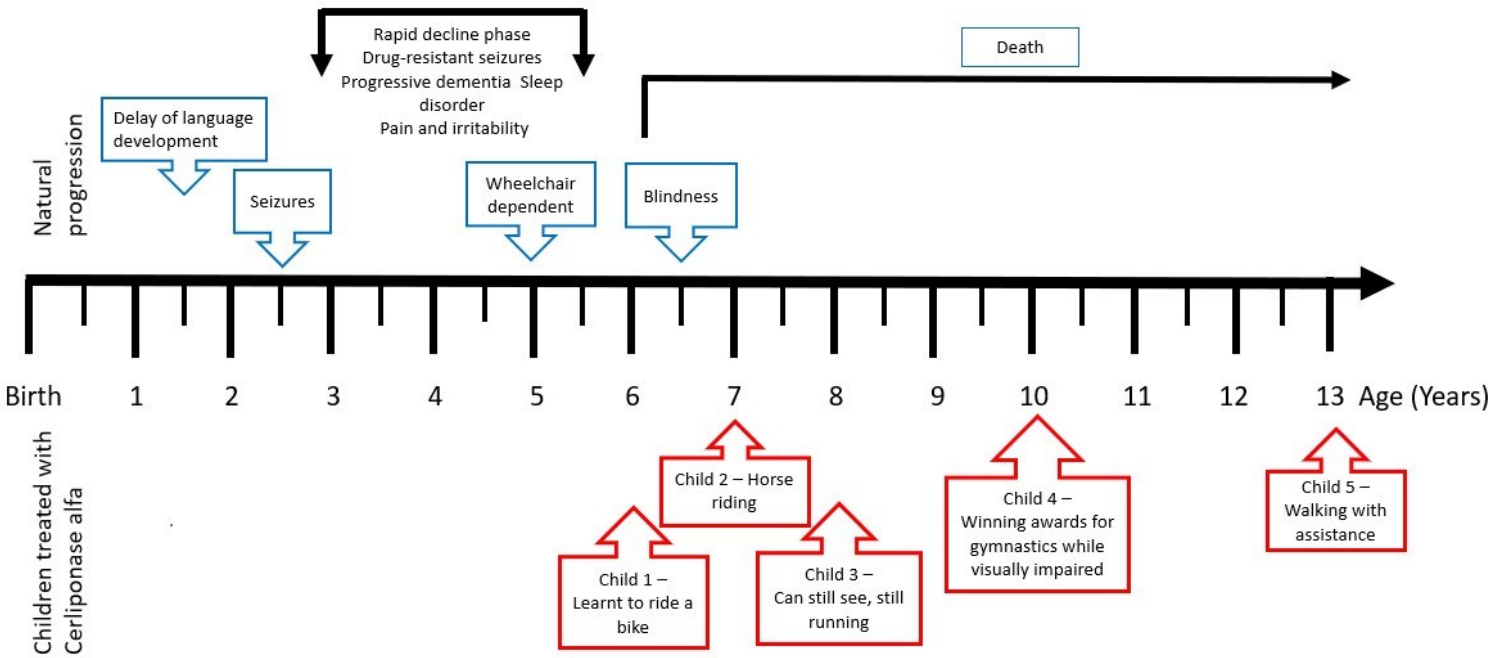



Figure 1: The red boxes represent activities that children, who are currently receiving Cerliponase alfa, can do aged 6-13 years old in comparison to data of children from the natural history study at the same age (blue boxes). Please watch the submitted videos to see some of these children in action.

Because parents reported that their children seemed to have better moods and concentration following their infusions, we asked teaching professionals for their opinions on the children during school hours. We asked how the children's ability to learn new skills, behaviour, attention span and engagement in play and self-care were affected on the days leading up to an infusion and the immediate days afterward (education survey Q50-70). These professionals noticed a negative effect in all areas before infusion and a positive effect post treatment. The biggest improvement was with the attention span:

| | |
|---|---|
| | • *"Prior to the infusion, this pupil is impacted greatly. They are unsettled, appear more distressed and less engaged in learning. The first day after the infusion, they are very tired but more relaxed. The few days after the infusion, they are very engaged, more excitable, more focused and alert in their learning."*<br><br>• *"This pupil is typically happier and achieves more educational targets in school post treatment."*<br><br>Furthermore, all responders who could compare between either a non-treated child who previously attended the school or a child who started treatment after joining the school, said they could see the difference treatment with Cerliponase alfa made to the children (education survey Q71-72):<br><br>• *"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."*<br><br>• *"The pupil who attended our setting with CLN2, prior to Brineura being available, had a much shorter and more negatively impacted life. Their physical abilities reduced rapidly, and they struggled with health and wellbeing."* |
| **12. What do patients or carers think are the disadvantages of the treatment?**<br>Please refer to the MAA re-evaluation patient submission guide | It is known that Cerliponase alfa does not stop vision loss as it does not cross the blood brain barrier. Parents are aware of this before starting treatment and it is a major source of anxiety. Fifty-two percent of the families feel that their child's eyesight has deteriorated since starting treatment (family survey, Q58). Furthermore, parents felt that there was an association between loss of mobility and eyesight, not due to progression of disease symptoms but caused by a lack of confidence in the child to navigate their now dark and unfamiliar world.<br><br>Of the families that responded, 26% had a reaction to treatment reporting symptoms ranging from a rash to anaphylaxis (family survey Q49). These have been managed through use of steroids prior to infusion. Less than 20% of parents reported side effects from the treatment such as tiredness, loss of appetite, sickness and high temperature. No-one has discontinued treatment due to reactions or side effects. When asked directly about the disadvantages of treatment, many parents spoke about the initial brain surgery, fear of device failure, infection in the device, tiring infusion days and the length of time in hospital every 2 weeks (family survey Q77):<br><br>• *"The fear of the device failing and not getting the full amount of the coveted drug. During infusion, keeping an eye on the child to make sure the accessed needle is not knocked out by my active child!"* |

| | |
|---|---|
| | • *"Juggling family life around a treatment which is every two weeks on the same day at the same time. However, this is minor and something that we cope with thanks to the support of family and friends."*<br><br>• *"Keeping her still for the 4 hours 12 mins."*<br><br>Another negative aspect was the stress associated with the fact the treatment could stop after the MAA. 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 ( family survey Q78):<br><br>• *"Without the treatment our daughter would be bed bound not able to walk talk or feed herself. Maybe she would have been blind or even dead. Thanks to treatment she can do all those things without struggling and she can enjoy her life."* |
| **13. What place do you think this treatment has in future NHS treatment and care for the condition?**<br>Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway. | Cerliponase alfa is the only treatment available that addresses the cause of the disease rather than managing the symptoms. It slows the progression of the disease and greatly affects the quality of life of the child and extended family and as such is irreplicable by any other treatment. Cerliponase alfa is administered within the specialist centres and multidisciplinary settings and accompanies well other treatments such as anti-epileptic and pain medication, physio and speech therapies.<br><br>Due to delayed diagnosis and a complete absence of specific care pathways for patients diagnosed with CLN2 as mentioned earlier, the BDFA feels that there is still a long way to go for the NHS to ensure that the children affected by CLN2 receive maximum benefit from the available treatments. |

# Section 4 Patients views on assessments used during the MAA

### Table 4 Measurements, tests and assessments

| | |
|---|---|
| **14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment.**<br>**How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?** | As per the MAA agreement, the data on clinical uncertainties such as CLN2 clinical rating scores over time, the frequency and severity of tonic-clonic seizures, myoclonus and dystonia control, visual acuity, extra-neurological symptoms, cause of mortality and quality of life were collected by clinical teams. The BDFA has not had access to these data and therefore we are unable to comment on measuring the clinical effectiveness of the treatment or addressing of uncertainties. Instead, a series of questions in our survey were used to assess the parents' viewpoints on the MAA assessments.<br><br>Parents were concerned that two major factors played a significant role in preventing the MAA tests and assessments to fully capture the effectiveness of treatment with Cerliponase alfa that they observed during the course of MAA:<br><br>Delay to diagnosis: The Batten community is anxious that delay to diagnosis and access to treatment will be unfairly reflected on the assessment of treatment with Cerliponase alfa. The BDFA therefore considers continuous delay to diagnosis of CLN2 as the most significant unmet need.<br><br>Because of the nonspecific nature of the presenting symptoms of CLN2 disease, there is often a diagnostic delay, which can result in delays to the provision of disease-specific treatment, including complex multidisciplinary care and Cerliponase alfa. There is strong evidence that early provision of care and access to Cerliponase alfa result in improved patient outcomes, including delaying or stopping the progression of the disease. The diagnostic delay in our surveyed cohort was between 3 months and 4 years, with 54% children waiting for more than 1 year and visiting more than 2 specialists (68%) to receive the diagnosis. Half of the families waited 3 months or longer for an appointment to see a specialist and felt that waiting times delayed getting a diagnosis and treatment (family survey Q11-21):<br><br>• *"The journey from symptoms to diagnosis was very distressing not knowing what was happening, I myself took the child to out of hours due to concern with walking declining and this ended up going to A&E and then being threatened with social services only to find out that it was the disease which was affecting her and nothing else. It took two years from first seizure to diagnosis, and we were told that she would live into her 80s which was obviously incorrect, the lack of support has been shocking but the teams at XXX hospital since being on treatment have been amazing and noticed a difference."* |

Despite the availability of Cerliponase alfa which has the potential to change the course of the disease and the fact that CLN2 can be diagnosed by simple enzymatic test, the BDFA has not seen any evidence of shortening the time of diagnosis during the 5 years of Managed Access Agreement (MAA).

Of the children identified in our survey, only 4 (13%) (family survey Q11) were identified as siblings rather than from symptoms highlighting the difficulties faced by parents trying to get a diagnosis. At least 5 children have been unable to access Cerliponase alfa due to being too far progressed with the disease at the time of diagnosis. Without an effective Newborn Screening programme, it is impossible to achieve earlier diagnosis as the symptoms are associated with more common childhood issues resulting in diagnostic blind alleys.

COVID-19 pandemic: Of the 17 responders who received a diagnosis during the pandemic period, 10 (59%) felt that diagnosis was delayed (family survey Q105).

- *"Our child's first major seizure was in May 2020 when she was 4. They said due to protocol with regard to COVID it was going to be impossible to let her have an MRI. Those services had been paused and they saw it as non-urgent. This changed within two months as seizures increased and we repeatedly landed in hospital. Once we blue lighted to the specialist hospital in Oxford there were no problems accessing MRI. In three months however, she had changed a lot and symptoms were coming thick and fast."*

Whilst Cerliponase alfa treatment continued, children with CLN2 disease also require a wide range of support services such as physical therapies, chiropractic, massage, and speech and language therapy; however, such services were largely stopped during the pandemic, causing families concern about deterioration in their children's condition. These services are often provided through specialist schools, but these were also closed. Families reported decline in their child's function/ability without this additional support, although they did see improvements once services resumed (Mortensen A et al, 2022 (available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8767529/, [accessed 10.10.2023])).

- *"I definitely think, during that big lockdown, that she lost a lot of skills, communication skills, motor skills, mobility. I just felt like I was watching her just deteriorate in front of my eyes. […] I bought all sorts. […] I just felt like I was watching her go downhill. I do feel better now that she can go to school."*

| | |
|---|---|
| **15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?** | When asked, 93% of parents (family survey Q82) stated that they had to make additional hospital visits outside of infusion day and the majority of these visits were related to the assessments required as part of the MAA. Some of these visits were considered to be unnecessary repetition and that they were too long. One parent said that eye assessments were unnecessary once a child has full vision loss.<br><br>Parents told us that assessments took place when their children were tired and did not want to cooperate. The impact of vision loss on the confidence and ability of a child to perform movements in an unfamiliar setting in front of strangers was not taken into account:<br><br>• *"The tiny snapshot of time that the assessors see our child and at a time when they are usually tired and in an unrelaxed/unfamiliar environment, never captures our child at their best."*<br><br>• *"The children aren't preforming monkeys. They don't want to engage with people they're unsure of and if it's a new setting they would rather explore and have a nosey then sit and do what they are asked."*<br><br>Parents felt that the psychology tests were inadequate asking for information the child would be unable to articulate (e.g. suicidal thoughts).<br><br>• *"The psychological tests were often done using pictures that were not very clear and often ones that did not interest our child. So, he was quite bored and therefore got marked as not knowing what a fork is (for example) even though he does know what a fork is."*<br><br>• *"I found the psychology assessment was the worst, they asked absolutely stupid questions, and it was just read off a sheet. Can they read "no" can they read a book" …. Unnecessary and not catered for. Would be helpful to get a Questionnaire together tailored for CLN2 children with a better understanding of their needs, ability's etc and maybe get it to be completed at schools or by professionals who see them on a daily basis and can fill that in on an overall basis and they're not judged if it's a bad day or good day on top."*<br><br>The parents understood that the tests were an important part of the assessment of the treatment but should not be the sole evidence as they are a snapshot of an often tired and uncooperative child. Instead, there should be an alternative method for capturing the effectiveness of treatment and the quality of their lives using videos from day-to-day activities and parent statements. |

| | |
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| **16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments?** If not please explain what was missing. | Some parents found the tests upsetting, stressful and inadequate:<br><br>• *"Assessments non uniform across centres/different professionals. Tests subjective. Too open to interpretation, little guidance for parents."*<br><br>• *"There were multiple instances where tests were repeated over and over again which was stressful for everyone due to the constant hospital visits."*<br><br>Some parents found retinal scans "emotionally tough." Another area of emotional difficulty for the parents was having to answer the psychology questions.<br><br>Parents have found the uncertainty of the process very difficult to cope with saying:<br><br>• *"Life changing treatments are widely available on NHS and people don't have to fight for the treatment to be available. But we do. And our children have gone through unnecessary tests that prove nothing, just cause upset and stress. Isn't it enough to be told that your child has terminal disease and there is treatment that can slow it down? Why do we have to fight for it. Isn't it human right of our children that if treatment is proven to be working it's unethical to even think of taking it away?"*<br><br>• *"It's been very traumatic waiting for this review, not knowing if a treatment that is keeping your child alive is going to be taken away. It's hard to understand how the benefits of Brineura are not obvious to NICE (especially in children diagnosed prior to 4yo) and our children deserve to live. Feeling like there is a price tag on your child's life is utterly heartbreaking."* |
| **17. What outcomes do you think have not been assessed or captured in the MAA data?** Please tell us why | Many parents in the survey felt that the MAA failed to accurately measure QOL. The tests are designed to look at what the children can't do, what skills they have lost rather than examine what they are still able to do and enjoy. For example, when a child has lost their sight, they will not be able to recognise letters, but the test doesn't assess a different method of letter recognition and therefore the child will lose points on the rating scale but may still retain the skill. This skews the clinical data.<br><br>The assessments may not have captured changes in the children such as sleeping and behaviour. Our parents reported: |

| | |
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| | • *"Our daughter began to show severe aggression prior to beginning Brineura. After approx 8 months of treatment, she was back to her old, very joyful self. Also, walking and communicating really improved around this time too."*<br><br>• *"Our son used to be unable to sleep, he is now able to sleep 12 hours a night without any need for any other medication other than the enzyme replacement infusions."* |

# Section 5 Patient population

### Table 5 Groups who may benefit and those who declined treatment

| | |
|---|---|
| **18. Are there any groups of patients who might benefit more or less from the treatment than others?**<br>If so, please describe them and explain why. | All parents who participated in the survey reported benefits of treatment with Cerliponase alfa which is backed up by the published literature.<br><br>Eighty-three percent of children who participated in the pivotal study with Cerliponase alfa had advanced disease with motor-language (ML) score 3 and 4 (out of a maximum of 6) on the CLN2 rating scale. Cerliponase alfa significantly slowed clinical decline in the overall study group compared to the similar natural history cohort (Schulz A et al, 2018 (available: https://www.nejm.org/doi/10.1056/NEJMoa1712649?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov [accessed 26.10.2023])).<br><br>In the UK there have been two patients with slower progressing CLN2 disease (atypical phenotype) who benefitted from treatment with Cerliponase alfa. Again, this has been backed up by evidence and published literature. In study conducted by Segura E et al (2021, available: "Real world effectiveness of cerliponase alfa in classical and atypical patients. A case series" - ScienceDirect [accessed 15.01.2024]), patients with atypical CLN2 phenotype showed clinical benefits when treated with Cerliponase alfa with no decline in the clinical status greater than 2 points on Hamburg, Weill Cornell and CNL2 clinical assessment scale. Wibbeler et al (2021, available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027928/ [accessed 09.01.2024]) reported that Cerliponase alfa has a potential to stabilise ML function in patients with atypical CLN2 phenotype.<br><br>There is strong evidence that early diagnosis results in improved clinical outcomes in asymptomatic children, including the affected siblings of previously diagnosed CLN2 patients. An asymptomatic patient treated with |

| | |
|---|---|
| | Cerliponase alfa for 2 years showed age-appropriate increase in Gross Motor Function Measure, increase in cognitive developmental age and without observed cerebral and cerebellar atrophy (Schaefers J et al, 2021 (available: https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01858-6 [accessed: 19.12.2023])). In another study involving 14 children diagnosed with CLN2, children who were diagnosed early with a maximum ML score of 6 (n=7) retained the motor and language function and remained at the same ML score after 140.4 (6.0) weeks of treatment (Schulz A et al, 2023, oral presentation (O56) at the International Congress of Neuronal Ceroid Lipofuscinoses, September 2023, Hamburg (https://ncl2023.de/wp-content/uploads/2023/09/NCL2023-Abstract-Book-27.09.pdf [accessed: 26.09.2023]). The parent of the child in the UK who was diagnosed asymptomatic as the sibling of her older affected sister and started early treatment with Cerliponase alfa said:<br><br>• *"Our daughter has the most incredible quality of life. She enjoys ballet classes, she rides her scooter, she loves going on walks & collecting leaves and sticks in the woods with our dog. She loves climbing and going to adventure playgrounds. She loves arts and crafts, painting, drawing and one of her other favourite activities is playing with her dolls and real-life play. Due to attending hospital since she was a baby, she loves pretending to be a nurse. She tells everyone that she wants to be a nurse when she grows up. Her memory is amazing. Her chatting and interaction is amazing, she is emotionally intelligent and is so loving. The life she leads would simply not be possible without Brineura. She is all the proof you need to see Brineura works. Her eyesight is amazing and she is able, agile, mischievous and full of glorious energy and character. We are able to enjoy family adventures, holidays etc. We have a comparison with our older daughter who could not walk, had never spoken, was tube fed and had a multitude of health needs at the age of 8."*<br><br>The BDFA therefore advocates for all children diagnosed with CLN2, regardless of their clinical status, to have uninterrupted access to Cerliponase alfa. |
| **19. Were there people who met the MAA eligibility criteria who decided not to start treatment?**<br>Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this. | N/A |

## Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

No

## Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

- Innovation: Cerliponase alfa is the first and only licensed specialist treatment for any type of Batten disease. It is a groundbreaking and life transforming treatment that directly addresses the cause of the disease by replacing the missing enzyme TPP1. It is a highly innovative treatment which is administered directly into the cerebrospinal fluid via intraventricular (ICV) infusions, resulting in widespread distribution to the affected areas of the brain. Cerliponase alfa was the first drug that was delivered via ICV infusions. Another innovative aspect of Cerliponase alfa are bi-weekly infusions which is significant improvement comparing many other enzyme replacement therapies which are administered weekly, thus providing greater convenience to patients and their families, and contributing to improved quality of life.

- Research evidence on patient or carer views of the treatment:

    - Malcolm C. *et al.* J Child Health Care. 2014 Sep;18(3):230-40. Available: https://pubmed.ncbi.nlm.nih.gov/23754839/ [accessed 01.12.2023].

    - Schulz A. *et al.* Journal of Inborn Errors of Metabolism & Screening 2020, Volume 8: e20190013 DOI: 10.1590/2326–4594–JIEMS–2019–0013. Available: https://discovery.ucl.ac.uk/id/eprint/10098316/ [accessed 21.10.2023].

## Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Despite 5 years of Managed Access Agreement for Cerliponase alfa, it is unacceptable that there is still a long delay to diagnosis, resulting in: a) children receiving the treatment when their disease has already progressed and b) potentially resulting in a false perception about the lack of treatment affect.

2. Progression of vision loss which cannot be addressed by Cerliponase alfa ICV infusions may have created a false impression about the lack of treatment effect despite families observing multiple benefits in terms of function and quality of life.

3. The COVID-19 pandemic resulted in some important treatments, which are part of important multi-disciplinary treatment approach, being made inaccessible thus potentially resulting in a false perception about the lack of treatment affect.

4. Families and teachers of affected children reported multiple benefits of treatment with Cerliponase alfa that could not be adequately captured by the MAA process.

5. Cerliponase alfa is the only available treatment that addressees the root-cause of CLN2 and therefore all children diagnosed with CLN2, regardless of their clinical status, must have uninterrupted access to Cerliponase alfa.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

BATTEN DISEASE FAMILY ASSOCIATION
Together we WILL make a difference
Registered Charity In England and Wales 1084908 - Scotland SC047408

**CLN2 Family Survey Introduction**

You have been asked to complete this survey because we understand that you are involved in the care of a child/children/young person(s)/younger adult(s) with a diagnosis of CLN2 Batten disease. Cerliponase alfa (Brineura) is a drug that is currently available as a treatment for the condition under a Managed Access Agreement with the NHS and its ongoing delivery is subject to a final approval by the National Institute for Health and Care Excellence (NICE).

The purpose of this survey is to gather relevant information to accurately fill in the patient advocacy form for submission to NICE as part of the re-evaluation of Brineura. As a patient advocacy group, the BDFA are charged with gathering data relating to the families' experiences of CLN2 and the treatment options available. During the resubmission process NICE will be looking at the clinical data gathered by the drug company BioMarin and the clinicians, but we contribute to the decisions made about treatments by sharing your voices and helping the committee to understand the real world, the lived experience of CLN2 Batten disease and Brineura. This will include the negative as well as the positives of the treatment. Because this data is for the resubmission, we are asking you to complete this questionnaire because you can provide valuable information about the life of an affected child/children/young person(s)/younger adult(s) in your care with a confirmed diagnosis of CLN2 Batten disease.

We recognise the emotional difficulty of adding comments in some of the "further information" sections of this questionnaire but, where appropriate, we would be grateful if you could complete those sections as they are often of great value to us in highlighting the real-life experiences of those contributing to the care, wellbeing, and education of young people with CLN2. We have a limit on how much we can send to NICE so not everyone's comments and testimonies can be used but we need to accurately represent your experiences.

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**Confidentiality**

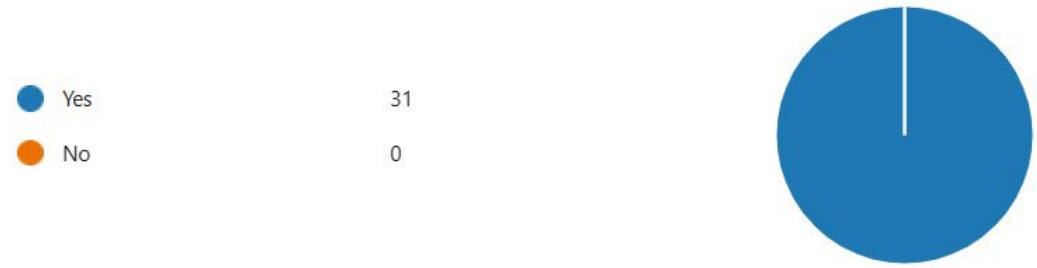
The survey and the data stored is completely anonymous. Once the report is created with the cumulative data, it will not be possible to identify any particular family, even for the BDFA. The survey questions, data, and report will be available to anyone once published on the NICE website hence the need for confidentiality.

The photos/videos will be available to the committee. We will endeavour to maintain the privacy of your family wherever possible but please consider this when selecting photos or videos to share with us. We want to show your child/children/young person(s)/younger adult(s) living their lives without compromising their safety or dignity.

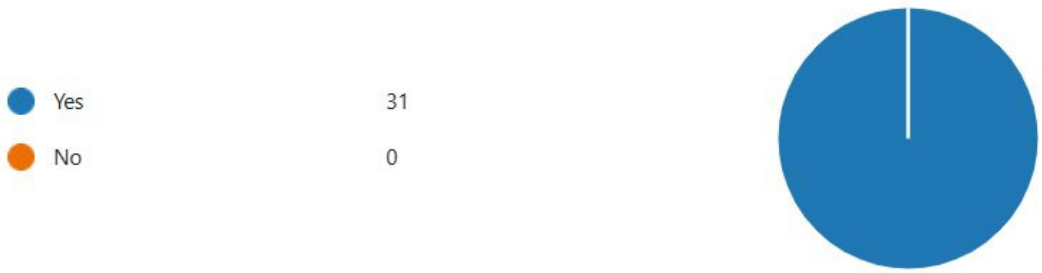
The survey should be completed per child/children/young person(s)/younger adult(s) that you care for. If you have more than one child/children/young person(s)/younger adult(s) with CLN2 Batten disease, please fill out a separate survey for that child/children/young person(s)/younger adult(s). Please encourage anyone over the age of 18 years who has caring responsibilities within your extended household to fill out the survey too, the more answers we have, the more accurate the data becomes.

Your participation in this survey is entirely voluntary and you ***do not have to answer any questions you do not want to***. We need your consent to process this information. If you are happy for us to use your information from this survey, please place a cross (x) the consent box below and confirm you are over the age of 18.

I consent to the information I provide by filling in this survey to be used by the BDFA.




I am over the age of 18 years.

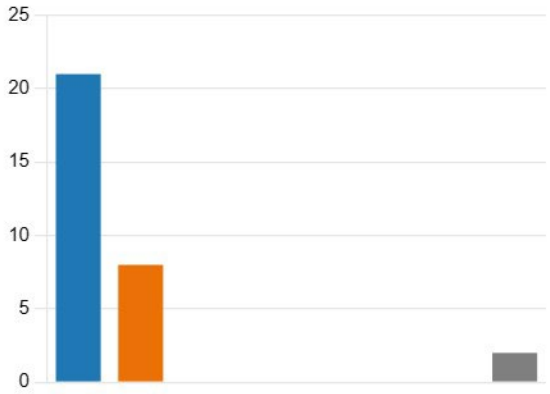


**PART 1**

**About You**

4) What is the relationship between you and the child/children/young person(s)/younger adult(s) you are caring for?

| | |
|---|---|
| Mother | 21 |
| Father | 8 |
| Grandmother | 0 |
| Grandfather | 0 |
| Sibling (18+) | 0 |
| Guardian | 0 |
| Other | 0 |
| Other | 2 |




5) Which geographical part of the UK do you live in?

| | |
|---|---|
| England | 27 |
| Northern Ireland | 2 |
| Scotland | 0 |
| Wales | 2 |



**PART 2**

**The Patient**

6) How many child/children/young person(s)/younger adult(s) in your household have had a confirmed diagnosis of CLN2 Batten disease?

| | |
|---|---|
| One | 24 |
| Two | 7 |
| Three | 0 |



IMPORTANT NOTE: Please complete a separate survey for each affected child/young person/younger adult you care for.

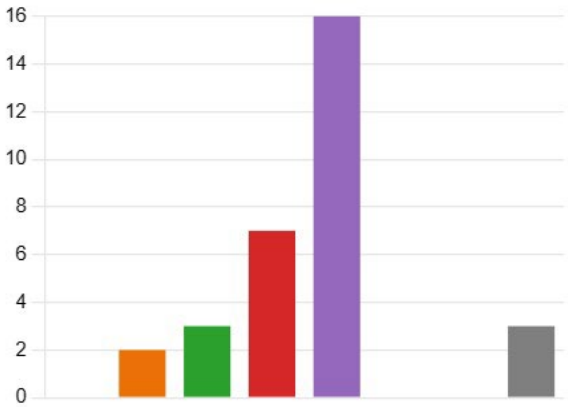
7) How old is the child/young person/younger adult you are completing this survey for?

| | |
|---|---|
| 0-3 years | 1 |
| 4-7 years | 17 |
| 8-11 years | 7 |
| 12+ years | 6 |



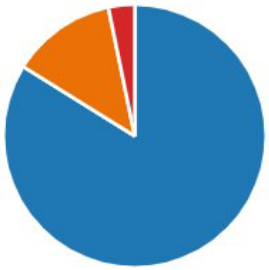
8) What age was the child/young person/younger adult in this survey when the CLN2 diagnosis was confirmed?

| | |
|---|---|
| 0 - <1 | 0 |
| 1 - <2 | 2 |
| 2 - <3 | 3 |
| 3 | 7 |
| 4 | 16 |
| 5 | 0 |
| 6 | 0 |
| 7+ | 3 |



9) Where do you receive specialist care?

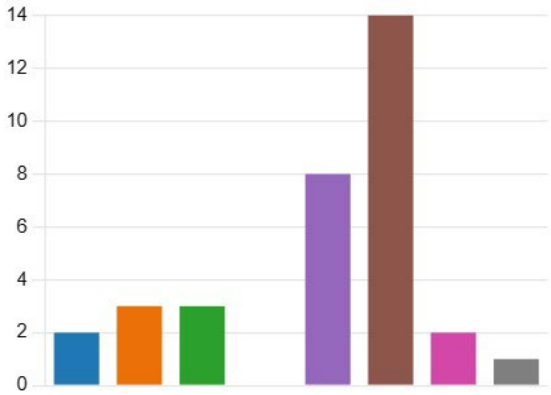
| | |
|---|---|
| Paediatric Metabolic Services in ... | 26 |
| Metabolic Services in Northern I... | 4 |
| Other (please specify) | 0 |
| Other | 1 |



Other: Adult metabolic services

10) Which treatment centre do you/did you receive Brineura at?

| | |
|---|---|
| Belfast | 2 |
| Birmingham | 3 |
| Bristol | 3 |
| Glasgow | 0 |
| GOSH | 8 |
| Manchester | 14 |
| Newcastle | 2 |
| Salford | 1 |



**PART 3**

**Diagnosis of CLN2**

11) Was the child/young person/younger adult in this survey diagnosed from symptoms or by genetic testing as a sibling?
    a) Symptoms
    b) Sibling

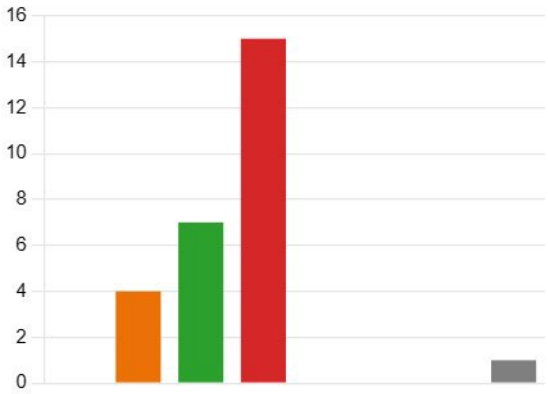
| | |
|---|---|
| Symptoms | 27 |
| Sibling | 4 |



The following 11 questions relate to the initial diagnosis of the first affected child/children/young person(s)/younger adult(s) in a family. If you have more than one affected child/children/young person(s)/younger adult(s) and are completing this survey for a younger sibling diagnosed through genetic testing, please do not complete the following section but move to question 13 of PART 3.

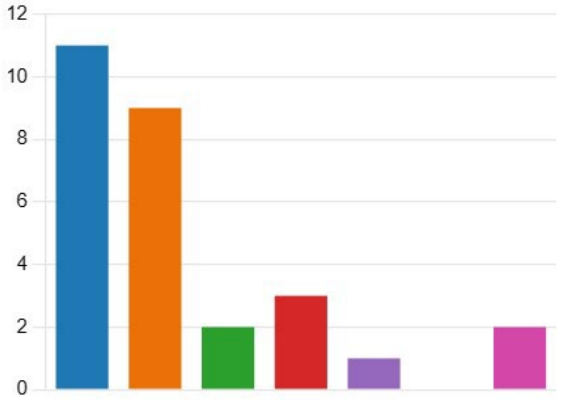
12) How old was the child/young person/younger adult in this survey when you first noticed symptoms?

| | |
|---|---|
| 0 - <1 | 0 |
| 1 - <2 | 4 |
| 2 - <3 | 7 |
| 3 | 15 |
| 4 | 0 |
| 5 | 0 |
| 6 | 0 |
| 7+ | 1 |



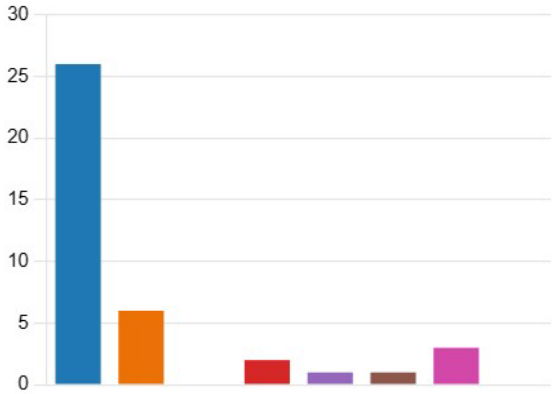
13) Which of the following symptoms did you notice first?

| | |
|---|---|
| Seizures | 11 |
| Language delay | 9 |
| Delayed motor development | 2 |
| Falls | 3 |
| Loss of language | 1 |
| Loss of motor skills | 0 |
| Other (please specify below) | 2 |



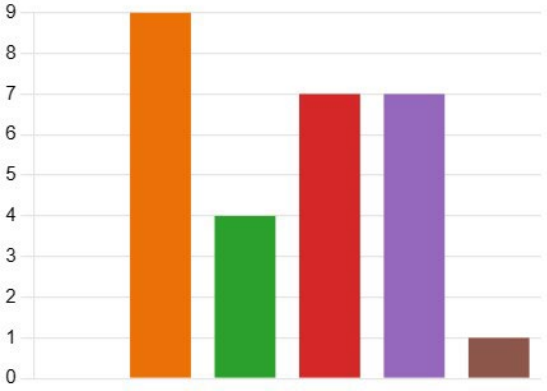

14) Who made you aware of these symptoms (please select all that apply)?

| | |
|---|---|
| Myself | 26 |
| Family member | 6 |
| Friend | 0 |
| Early years provision | 2 |
| Primary school | 1 |
| Primary healthcare (e.g., midwif... | 1 |
| Secondary healthcare (A and E, ... | 3 |
| Specialist centre | 0 |



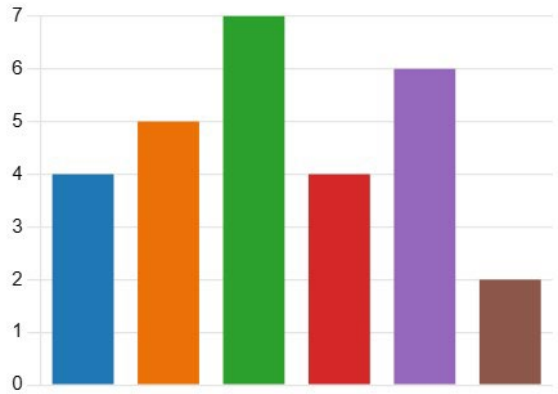

15) After noticing symptoms, how long did it take to get a confirmed diagnosis of CLN2 Batten disease?

| | |
|---|---|
| Less than 3 months | 0 |
| 3 – 6 months | 9 |
| 7 – 12 months | 4 |
| 1 - 2 years | 7 |
| 2 - 4 years | 7 |
| More than 4 years | 1 |



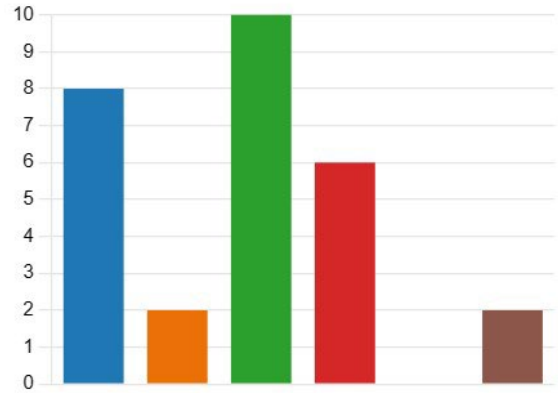
16) How many specialists did you see before receiving a confirmed diagnosis?

| | |
|---|---|
| 1 | 4 |
| 2 | 5 |
| 3 | 7 |
| 4 | 4 |
| 5-9 | 6 |
| 10+ | 2 |



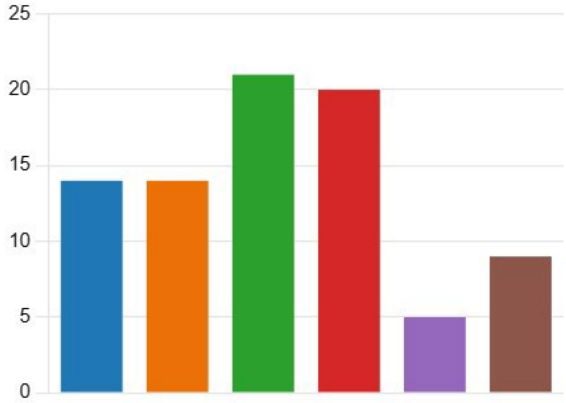

17) Which specialist were you first referred to?

| | |
|---|---|
| Speech therapist | 8 |
| Occupational health | 2 |
| Paediatrician | 10 |
| Neurologist | 6 |
| Other (please specify) | 0 |
| Other | 2 |



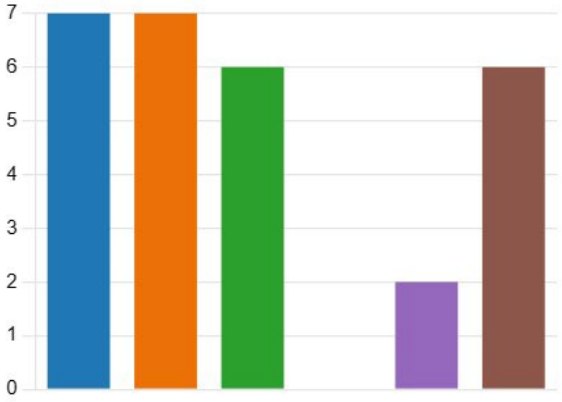

18) During your diagnostic journey, which other specialists were you referred to (please select all that apply)?

| | |
|---|---|
| Speech therapist | 14 |
| Occupational health | 14 |
| Paediatrician | 21 |
| Neurologist | 20 |
| Other (please specify) | 5 |
| Other | 9 |



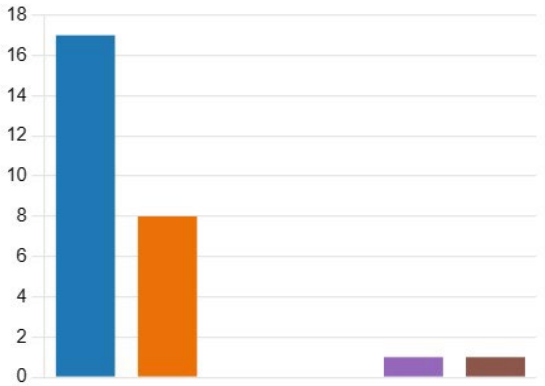
19) What was the longest time you can remember having to wait for an appointment to see a specialist while trying to get a diagnosis?

| | |
|---|---|
| 0 – 6 weeks | 7 |
| 6 weeks – 3 months | 7 |
| 3 – 4 months | 6 |
| 4 - 5 months | 0 |
| 5 – 6 months | 2 |
| Over 6 months | 6 |




20) What was the shortest time you can remember having to wait for an appointment to see a specialist while trying to get a diagnosis?

| | |
|---|---|
| 0 – 6 weeks | 17 |
| 6 weeks – 3 months | 8 |
| 3 – 4 months | 0 |
| 4 - 5 months | 0 |
| 5 – 6 months | 1 |
| Over 6 months | 1 |




21) Do you feel these waiting times delayed getting a diagnosis and treatment?

| | |
|---|---|
| Yes | 17 |
| No | 7 |
| Don't know. | 4 |



22) Has the diagnosis of CLN2 Batten disease changed your decision whether to have further children? Please use the space below to help us understand this decision and what assistance you were offered.

| | |
|---|---|
| 1 | Yes. We don't want any more children. |
| 2 | No, we have since had another child who was tested within the womb. We have always wanted a big family; we were not put off by a diagnosis of Batten Disease. The support given by Manchester Royal in getting genetic testing in the womb was grateful received. Our daughter was born the picture of health and is truly a gift. |
| 3 | No - We had our children well before diagnosis. |
| 4 | We didn't wish to have any more children as I have a teenager already. |
| 5 | No |
| 6 | No |
| 7 | No, I already have a stepdaughter and with second child had the snip. Even with diagnosis at 39 I didn't want to have any more children. |
| 8 | No |
| 9 | No. I had already decided prior to diagnosis that I would not have any more children. Mostly due to my age. |
| 10 | The child's father and I have looked into genetic testing ourselves but the risks for us are low due to the chances of me having the same gene. |
| 11 | Yes. Because we have a neuro-typical child first, we would have to pay for private IVF/sperm washing which is just too expensive; and we couldn't go through the emotional rollercoaster of conceiving naturally and then terminating the child. |
| 12 | After learning my daughter was diagnosed with CLN2 I was very hesitant on having any kids in the future. My decision has since changed after speaking with relevant genetic support professionals. |
| 13 | This is too difficult to answer and a very personal matter due to lots of factors. |
| 14 | Yes |
| 15 | Yes. We were told that the options to go for IVF were expensive as we already had an unaffected child, we wouldn't get any funding through the NHS. We also felt that life was so very full, and we were struggling to keep it balanced as it was that to have a baby might disrupt the dynamic. It is still a heartbreaking decision for me that we haven't had more children. I can still dream of it. |
| 16 | Yes - it would be impossible to have further children. I wish we could, but it would be too difficult. |
| 17 | It did and was an extremely hard decision to make. Down to the fact of further children possibly having the condition and to how would we cope. We did however have another child after we had our diagnosis, we were able to test for it early on in pregnancy so that helped a lot. Our decision was made to have another child at the time we did as our second child with CLN2 is still very independent and does most things herself so our thought process was we do it now when we only have 1 wheelchair to get out with and it will be easier to manage. |
| 18 | We have not been offered assistance on this matter but have decided not to have other children for the risk of having CLN2. |
| 19 | We have had another child through PGT. |

| | |
|---|---|
| 20 | No |
| 21 | Not possible for us to have further children. |
| 22 | Yes 100%. We will never have any more children. |
| 23 | Yes, it was only after the diagnosis of my first child that we decided to have another child and went through the process of PGD to prevent this condition in him. |
| 24 | Answered on [redacted] questions. |
| 25 | Originally yes, we had decided no more but have now changed our minds and we would like to have another, but we are unable to afford IVF. We have decided to try naturally. I've not asked for any assistance as yet. I am struggling to get pregnant due to PCOS. |
| 26 | No, it hasn't but I am a single mum and no longer with son's bio father so due to the chances of me meeting another carrier I know would be hard but I do continue to be single and devote my life to my child |
| 27 | After giving birth to this child, I haven't been planning to have more children. |
| 28 | No, we'd get the embryo tested. |

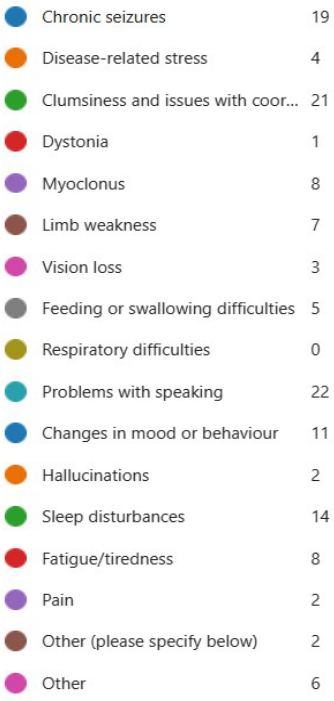
23) With regards to your and the child/children/young person(s)/younger adult(s) in this survey's diagnostic journey experience, if you would like to, please use your own words to provide further information below.

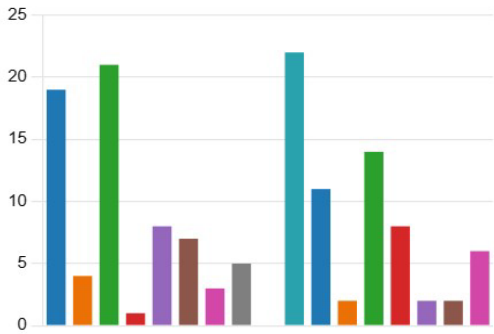
| | |
|---|---|
| 1 | Our first symptom was a speech delay, something which is common in young children. Our son was referred to a speech and language therapist, even with months of hard work his speech did not improve. He was clumsy on his feet, but our health visitor said he was just a boy and there was nothing to worry about. At three and a half years our son started having seizures, at first these were put down to febrile convulsions due to him being unwell, but it soon became apparent that these seizures were much more than just that. As our son continued to have seizures, we attended our local hospital where doctors had no clue as to what was happening to our child. It took for us as parents to take our child out of A&E and drive to another more specialised hospital. Once arriving at this hospital this is where the appropriate testing started to take place. We believe that time was wasted attending our local hospital. The specialists were not available. From our son's first seizure to diagnosis, it took 5 months, which to be diagnosed with Batten disease is quick. We believe that this is because the neurologist we were able to see by moving hospitals had previous experience with Batten Disease. She knew the signs, symptoms and therefore new what to test for. |
| 2 | An initial diagnosis of dyspraxia stopped any further attempts to diagnose for around 2 years, until symptoms worsened |
| 3 | Our paediatrician refused for many months to refer us to a neurologist because our child did not suffer from seizures. This delayed the diagnosis for at least a year. Eventually we only got referred to a neurologist by getting a referral from a family member who was a neurologist. However again the neurologist did not diagnose our child for at least a year as he did not have seizures and so he did not test for Batten disease. The MRI which was done quickly upon referral did show signs of Batten disease however this was not picked up by the team at our local hospital. |
| 4 | Tough journey to diagnosis. Really moved on when she had seizures then further tests. All over a 3-month period. |

| | |
|---|---|
| 5 | After the diagnosis of our daughter's older sibling. Our other three siblings were all tested for CNL2 Batten Disease. We were not offered this initially or even told that Batten Disease was genetic, we had to find this out through researching. We than had to ask for genetic testing. |
| 6 | Everything moved too slow. In case of CLN2 time is a factor how much we save. |
| 7 | Initially went to GP for speech regression, then falling/ataxia. Referred to SALT and paediatrician. Waited for months. Connie started having seizures in meantime. Hospital paediatrician linked the seizures with the regression and fast-tracked neurological assessments etc |
| 8 | The journey from symptoms to diagnosis was very distressing not knowing what was happening, I myself took the child to out of hours due to concern with walking declining and this ended up going to A&E and then being threatened with social services only to find out that it was the disease which was affecting her and nothing else. It took two years from first seizure to diagnosis, and we were told that she would live into her 80s which was obviously incorrect, the lack of support has been shocking but the teams at [redacted] hospital since being on treatment have been amazing and noticed a difference. |
| 9 | [redacted] was diagnosed during covid and so the only thing that we didn't get so quickly was an MRI scan. She the only thing that took time was the genetic testing that had to wait for a batch of tests in order to move forward. We had to wait 2 months for genetic tests to come back |
| 10 | Very frustrating. No one believed me as mother. |
| 11 | As our child started with more severe symptoms during the pandemic (seizures), she was unable to have an MRI done under GA as was our local hospital's procedures around isolating. If an MRI had been done sooner, we would have had an earlier diagnosis. |
| 12 | We had 2 genetic panels tested for [redacted], Battens never shown up once as it isn't tested for on a basic genetic testing! When Battens was specifically tested for, the neurologist at the local hospital forgot to put it on the test the first time, then one got lost and the last one we did he forgot to process…. This was until his sister started with seizures at exactly the same age of 3 and another doctor from Wales picked up on the connection due to seeing both siblings and raised the concerns of Battens and tested her. |
| 13 | We feel like it was the worst two years of our lives. We knew something wasn't right with [redacted] but don't feel like anybody listened, he was misdiagnosed with 'dose syndrome' which he did not have, then we battled with ongoing appointments for another 18 month after that false diagnosis. He went through a lumber puncture, MRI scans and blood tests, until we finally got his diagnosis 2 years later. It was only by chance we saw a doctor who was treating a boy with CLN2 and recognised the symptoms, I honestly feel if we hadn't seen that specific doctor, we still would not of got the diagnosis. |
| 14 | COVID delayed genetic testing results but eventually my daughter was prioritized because I was pregnant. She has an additional condition that causes developmental delay, so her learning difficulties were picked up earlier than a typical CLN2 child. |
| 15 | My son was 3 years old when he got diagnosed with CLN2, he suffered with late walking but didn't know it was because of the illness we just thought he was a lazy child. He started to walk around 23-month-old, and it was on his tip toes. Then at 3 he started haven seizures he had about 6 with around 7-10 days apart. He then had some test done MRI scans and lumbar puncture and it came back that he had CLN2 we got the results |

| | |
|---|---|
| | back about a month time and then got booked in for his operation for the treatment this was 3 days after finding about the illness. |
| 16 | It was a very long and scary time waiting for the diagnosis. Our team at [redacted] Hospital were incredibly and put [redacted] forward for every test from MRIs to CT scans and of course genetics. |
| 17 | Our daughter was the youngest child in the world to start treatment having been diagnosed at just 15months old because of her older sister's diagnosis (her older sister was 4.5yrs when she was diagnosed). Starting treatment at 21months old and now being 8 years old - if you met our daughter, you would never know she had Batten disease. She is walking, talking, dancing, singing, scootering living proof that Brineura is effective and is undoubtedly worth funding. It has given our daughter the chance of leading a healthy life, a prolonged life, a life filled with opportunities that without Brineura would never have been possible. |
| 18 | Our son's epilepsy gene panel results were delayed (the results took 8 months) due to covid and panel tests results being delayed. Also, first doctor did not link the seizures with delayed speech and MRI results (the base of his brain was small for his age) together which would have resulted in an earlier diagnosis. |

24) Before starting treatment, did the child/young person/younger adult in this survey experience any of the following symptoms (please select all that apply)?



Other:

Learning difficulties

Ataxia

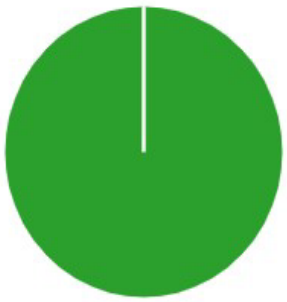
As with others, my child had 1 major seizure, his first from then on before diagnosis he had another 5 under 3 mins with no rescue medication or admitted to hospital. He then had a 6 min seizure 18 months into treatment and 1st time having rescue medication and taking to hospital to be allowed home a few hours after. This was his last seizure in Feb 2016 after 2 years on treatment. Now 9 years on treatment and seizure free for over 7 years.

**PART 4**

**Treatment**

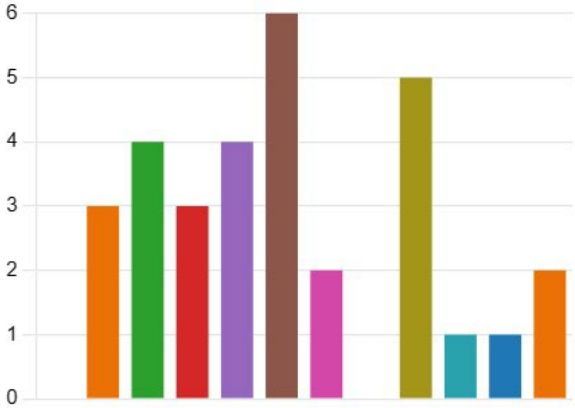
25) Has the child/young person/younger adult in this survey received treatment with Brineura (cerliponase alfa)?

| | |
|---|---|
| No | 0 |
| No, currently waiting to start. | 0 |
| Yes, currently receiving treatment. | 31 |
| Yes, treatment discontinued. | 0 |



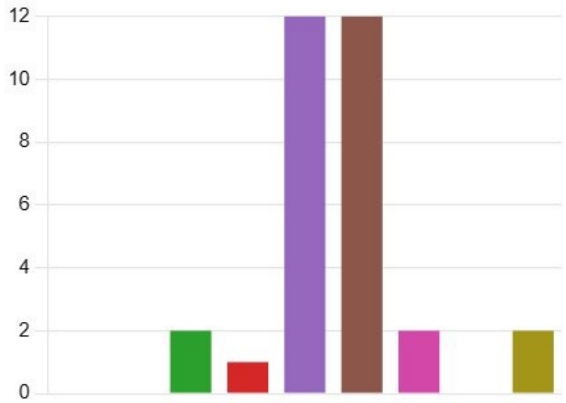
26) If the child/young person/younger adult in this survey is receiving Brineura, how long have they been receiving treatment?

| | |
|---|---|
| Less than 3 months | 0 |
| 3 – 6 months | 3 |
| 7 – 12 months | 4 |
| 1 - 2 years | 3 |
| 2 - 3 years | 4 |
| 3 – 4 years | 6 |
| 4 – 5 years | 2 |
| 5 – 6 years | 0 |
| 6 – 7 years | 5 |
| 7 – 8 years | 1 |
| 8 – 9 years | 1 |
| More than 9 years | 2 |



27) If the child/young person/younger adult in this survey has received Brineura, how old were they when they started?

| | |
|---|---|
| Less than 6 months | 0 |
| 7 – 12 months | 0 |
| 1 - 2 years | 2 |
| 2 - 3 years | 1 |
| 3 - 4 years | 12 |
| 4 – 5 years | 12 |
| 5 - 6 years | 2 |
| 6 – 7 years | 0 |
| More than 7 years | 2 |




28) Has the child/young person/younger adult in this survey ever received anti-epilepsy drugs?

| | |
|---|---|
| Yes, currently | 28 |
| Yes, previously | 0 |
| Never | 3 |



29) Has the child/young person/younger adult in this survey ever received sedatives?

| | |
|---|---|
| Yes, currently | 7 |
| Yes, previously | 6 |
| Never | 17 |



30) Has the child/young person/younger adult in this survey ever received painkillers?

| | |
|---|---|
| Yes, currently | 8 |
| Yes, previously | 12 |
| Never | 11 |



31) Has the child/young person/younger adult in this survey ever received botox?

| | |
|---|---|
| Yes, currently | 1 |
| Yes, previously | 2 |
| Never | 28 |



32) Has the child/young person/younger adult in this survey ever received other treatment (please state the type of treatment(s) below)?

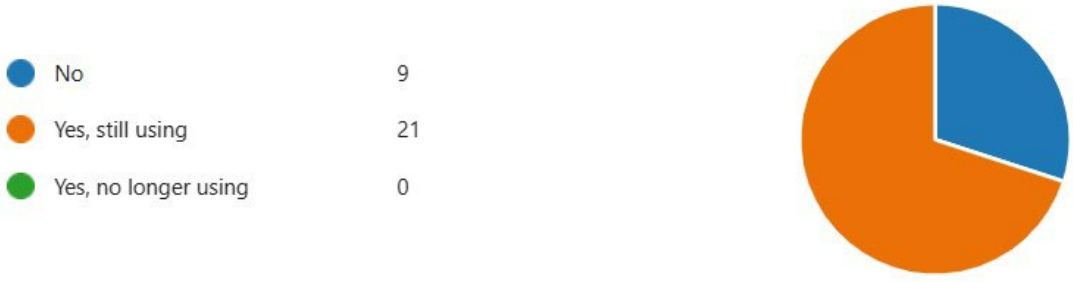
| | |
|---|---|
| Yes, currently | 0 |
| Yes, previously | 1 |
| Never | 18 |
| Other | 11 |



33) In response to your answers to Q28-32, if you would like to, please use your own words to provide further information below.

| | |
|---|---|
| 1 | Our son receives pain relief for muscle spasms that happens within his legs. This is also we're he receives Botox injections every four months. |
| 2 | Our daughter does not suffer with any sleep problems. |
| 3 | The child has been on several different anti-seizure medications and is now on a various mixture of medication but still having myoclonic seizures, absent seizures, and jerks. |
| 4 | My daughter is currently taking multiple AEM's to control her epilepsy alongside Brineura therapy. |
| 5 | Mickey button fitted shunt fitted |
| 6 | While our child is on anti-epileptic drugs, we only seen her have one seizure which was triggered by lights in an ophthalmology assessment. After about 5 months of being on Brineura, her seizures stopped. |
| 7 | Since starting treatment [redacted] is now 7, he is still eating everything we eat, he isn't in nappy's and still uses the toilet fully (day and night) he's still able to ride a motorbike on his own , he is still able to tell us what he wants "I want cheese" I want bike" he still has quite a lot of words to use, although his vision isn't really their anymore he still manages to get around comfortably in familiar places, he doesn't sit still he's always up and off, he can get up the stairs on his own, he can get up and down of the floor on his own, he is very very clever and doesn't forget a thing ! I honestly believe, pretty much know, that without this treatment he wouldn't be where he is today. He is absolutely amazing, and we push him so much to keep him doing what he does to get the most from our treatment! |
| 8 | Painkillers only for things not related to CLN2. Like for fever, immunizations etc. |
| 9 | He's been on treatment since June 2022, and he only has paracetamol when haven his infusion and antihistamine. We have all noticed since been on treatment his balance is a lot better and his speaking has improved. |
| 10 | Extra information regarding Q30. Our daughter has had painkillers but only Calpol as a general painkiller. |
| 11 | My child has been the same very low amount of epilepsy drugs and also sedatives and has for a long time even with big growth as he is becoming a teen it hasn't affected him as infusion helps him. |

34) Has the child/young person/younger adult in this survey required the use of a wheelchair?



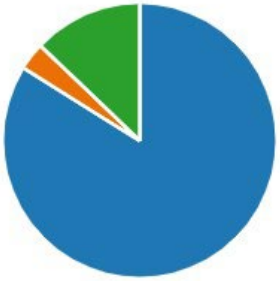
35) Has the child/young person/younger adult in this survey required the use of a walker?

| | |
|---|---|
| No | 10 |
| Yes, still using | 16 |
| Yes, no longer using | 5 |



36) Has the child/young person/younger adult in this survey required the use of a different walking aid?

| | |
|---|---|
| No | 26 |
| Yes, still using | 1 |
| Yes, no longer using | 4 |



37) Has the child/young person/younger adult in this survey required the use of a hoist?

| | |
|---|---|
| No | 23 |
| Yes, still using | 8 |
| Yes, no longer using | 0 |



38) Has the child/young person/younger adult in this survey required the use of a sleep system?

| | |
|---|---|
| No | 28 |
| Yes, still using | 3 |
| Yes, no longer using | 0 |



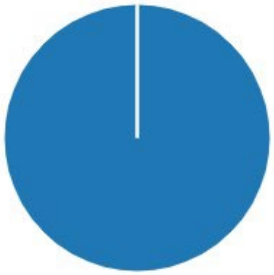
39) Has the child/young person/younger adult in this survey required the use of splints?

| | |
|---|---|
| No | 16 |
| Yes, still using | 10 |
| Yes, no longer using | 5 |



40) Has the child/young person/younger adult in this survey required the use of a ventilation support?

| | |
|---|---|
| No | 31 |
| Yes, still using | 0 |
| Yes, no longer using | 0 |



41) Has the child/young person/younger adult in this survey required the use of a communications device?

| | |
|---|---|
| No | 27 |
| Yes, still using | 1 |
| Yes, no longer using | 3 |



42) Thinking about the day of the treatment, how long does it take to travel to your treatment centre?

| | |
|---|---|
| 0 – 30 minutes | 4 |
| 30 - 60 minutes | 10 |
| 1 – 2 hours | 12 |
| 2 - 4 hours | 4 |
| More than 4 hours | 1 |



43) How do you travel to your treatment centre (please select all that apply)?

| | |
|---|---|
| Car | 27 |
| Bus | 2 |
| Train | 6 |
| Taxi | 4 |



44) Does receiving treatment mean you have to spend a night away from home?

| | |
|---|---|
| Yes | 2 |
| No | 28 |



45) On the day of treatment are you given a specific time for the infusion to start?

| | |
|---|---|
| Yes | 22 |
| No | 9 |

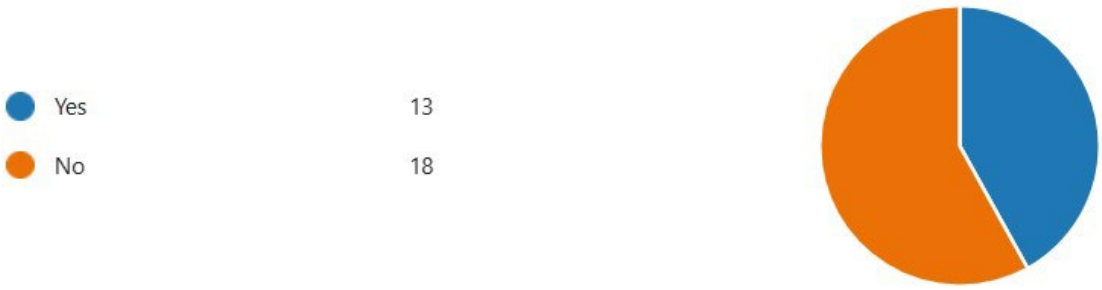


46) How often is that start time delayed?

| | |
|---|---|
| Never | 4 |
| Rarely | 12 |
| Sometimes | 9 |
| Often | 3 |
| Regularly | 3 |



47) Does this affect your journey time home?

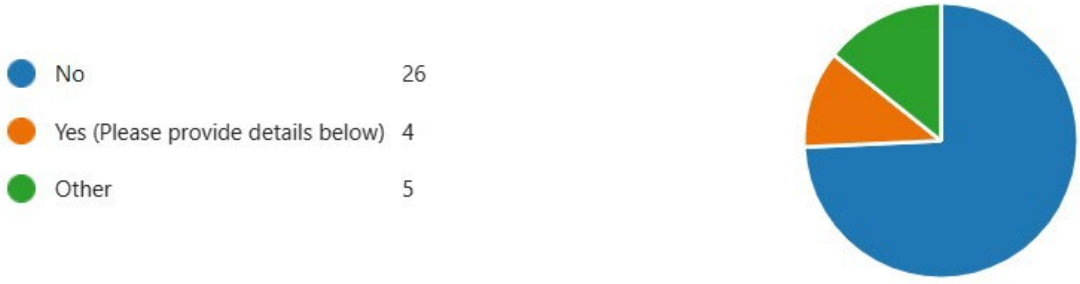



48) In response to your answers to Q42-Q47, if you would like to, please use your own words to provide further information below.

| | |
|---|---|
| 1 | We stay the night in London in GOSH hotel when there for eye treatment. We travel by train. Infusions in Manchester we travel by car. Treatments are never on time, and we often come back home at night |
| 2 | For just over five years we travelled from Manchester to London every two weeks to attend Great Ormond Street Hospital for treatment. At the start of this process, we would have to travel the night before and stay over in patient accommodation, we would then spend the day in hospital having treatment and then spend overnight in hospital for observations. As time went on this reduced to only an overnight stay the night before treatment, although we would arrive home late at night after treatment. We would travel via train and taxi to GOSH. During Covid we were unable to take the train or stay overnight the night before treatment. We would therefore get up at 2am to start the 5-hour drive to London for treatment. We would spend the whole day in hospital before making the 5-hour drive home. It was extremely tiring but something we never once questions ourselves doing as our children needed treatment and we were just so grateful that even during a global pandemic we were able to continue with the treatment our children needed to stay alive and healthy. |
| 3 | Fixed arrival time on treatment day, but time infusion starts is dependent upon when drug is taken from refrigeration and then availability of person accessing that day |
| 4 | We start at 10:30 and are quite slick with getting started at a good time. Being in Manchester it's generally rush hour when we finish so traffic is the issue not the treatment times. |
| 5 | Opening the centre in Manchester has massively improved our lives. Previously we travelled from Leeds to London. An overnight stay was always required. Now, we can be there and back in the same day with minimal disruption to family/home life. |
| 6 | The child stays between different households, she will stay with myself and her father on weekends and to help with treatment and then with her mum and gran in the week. Travel time varies depending on who's house she is in as we live in different counties, we are closer than her mum and our travel time is between 50 minutes or an hour and then 90 minutes to take her home to her gran after treatment, we are told to be there for 9am and will call when leaving home for the Brineura to be defrosted which is often |

| | |
|---|---|
| | not defrosted by the time we get there, treatment has never started at 9am it is usually between 9:45-10:30 this then impacts on the travelling and have had a few parking tickets due to staying over the free 6 hours you have at the hospital. |
| 7 | [redacted] has Melatonin as needed to help sleep. [redacted] uses a standing frame daily at school for 30-60 mins. We get into Bristol for 8:45am, and then infusion can start anywhere between 10:30am and 12pm. |
| 8 | My daughter lives between myself and my ex-partners home, so travel time does vary and increases regularly. |
| 9 | She loves travelling. |
| 10 | We get to our local hospital at around 10.30 and get our checks and green light from the doctors. Once this is done the children have their sedation and go to sleep, once their asleep we get straight on with infusion. There isn't a set time as it depends how long the kids take to settle but we usually leave around 4.30/5oclock just in time for tea on the way home! |
| 11 | He can walk but not far, so he only uses it when needed, like if we are out for a full day. He used to have splints when he first started walking to keep his feet flat. |
| 12 | It takes us usually about 1.5hrs to get to Manchester and more on the way home traffic dependent |
| 13 | We travel to hospital with hospital ambulance transport. On return journey there is often delays in getting the transport and we have to wait sometimes for 1-2 hours at the transport desk causing severe delays in getting home. |
| 14 | We are not given a specific start time but we are given a window so we always know it will be within an hour. We are only a 15min drive from home, so it is not a problem if this is delayed. |
| 15 | Our son is very much used to his infusion day, he enjoys seeing his infusion buddy, knows his routine of the day, is relaxed and happy for the day. |

49) Has the child/young person/younger adult in this survey had an allergic reaction to treatment with Brineura?



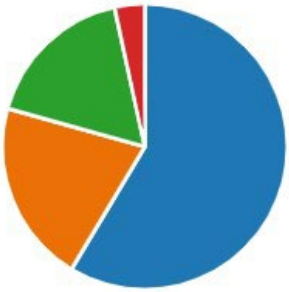
50) In your opinion, does the child/young person/younger adult in this survey suffer from any side effects from the treatment with Brineura?

| | |
|---|---|
| No | 28 |
| Yes (please provide details belo... | 2 |
| Other | 4 |



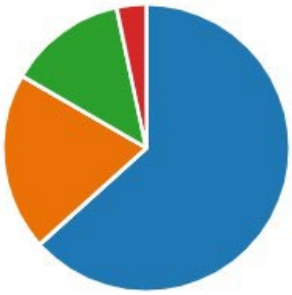
51) Since starting on Brineura, have you noticed any change in seizure severity?

| | |
|---|---|
| Major improvement | 17 |
| Minor improvement | 6 |
| No change | 5 |
| Minor deterioration | 1 |
| Major deterioration | 0 |



52) Since starting on Brineura, have you noticed any change in seizure frequency?

| | |
|---|---|
| Major improvement | 19 |
| Minor improvement | 6 |
| No change | 4 |
| Minor deterioration | 1 |
| Major deterioration | 0 |



53) Since starting on Brineura, have you noticed any change in seizure duration?

| | |
|---|---|
| Major improvement | 19 |
| Minor improvement | 2 |
| No change | 8 |
| Minor deterioration | 0 |
| Major deterioration | 0 |



54) Since starting on Brineura, have you noticed any change in clumsiness and issues with coordination, balance, and movement?

| | |
|---|---|
| Major improvement | 8 |
| Minor improvement | 4 |
| No change | 7 |
| Minor deterioration | 6 |
| Major deterioration | 6 |



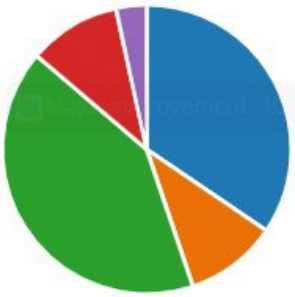
55) Since starting on Brineura, have you noticed any change in dystonia?

| | |
|---|---|
| Major improvement | 5 |
| Minor improvement | 0 |
| No change | 18 |
| Minor deterioration | 6 |
| Major deterioration | 1 |



56) Since starting on Brineura, have you noticed any change in myoclonus?

| | |
|---|---|
| Major improvement | 10 |
| Minor improvement | 3 |
| No change | 12 |
| Minor deterioration | 3 |
| Major deterioration | 1 |



57) Since starting on Brineura, have you noticed any change in limb weakness?

| | |
|---|---|
| Major improvement | 7 |
| Minor improvement | 2 |
| No change | 10 |
| Minor deterioration | 8 |
| Major deterioration | 4 |



58) Since starting on Brineura, have you noticed any change in vision loss?

| | |
|---|---|
| Major improvement | 0 |
| Minor improvement | 1 |
| No change | 14 |
| Minor deterioration | 7 |
| Major deterioration | 9 |



59) Since starting on Brineura, have you noticed any change in feeding or swallowing difficulties?

| | |
|---|---|
| Major improvement | 2 |
| Minor improvement | 1 |
| No change | 18 |
| Minor deterioration | 7 |
| Major deterioration | 3 |



60) Since starting on Brineura, have you noticed any change in respiratory difficulties?

| | |
|---|---|
| Major improvement | 2 |
| Minor improvement | 0 |
| No change | 27 |
| Minor deterioration | 1 |
| Major deterioration | 1 |



61) Since starting on Brineura, have you noticed any change in problems with speaking?

| | |
|---|---|
| Major improvement | 3 |
| Minor improvement | 6 |
| No change | 9 |
| Minor deterioration | 9 |
| Major deterioration | 4 |



62) Since starting on Brineura, have you noticed any change in changes in mood or behaviour?

| | |
|---|---|
| Major improvement | 12 |
| Minor improvement | 3 |
| No change | 13 |
| Minor deterioration | 3 |
| Major deterioration | 0 |



63) Since starting on Brineura, have you noticed any change in hallucinations?

| | |
|---|---|
| Major improvement | 3 |
| Minor improvement | 2 |
| No change | 24 |
| Minor deterioration | 1 |
| Major deterioration | 0 |



64) Since starting on Brineura, have you noticed any change in sleep disturbances?

| | |
|---|---|
| Major improvement | 6 |
| Minor improvement | 4 |
| No change | 19 |
| Minor deterioration | 2 |
| Major deterioration | 0 |



65) Since starting on Brineura, have you noticed any change in pain?

| | |
|---|---|
| Major improvement | 4 |
| Minor improvement | 0 |
| No change | 25 |
| Minor deterioration | 2 |
| Major deterioration | 0 |



66) Since starting on Brineura, have you noticed any changes in disease related stress?

| | |
|---|---|
| Major improvement | 5 |
| Minor improvement | 4 |
| No change | 18 |
| Minor deterioration | 4 |
| Major deterioration | 0 |



67) Since starting on Brineura, have you noticed any changes in tiredness or fatigue?

| | |
|---|---|
| Major improvement | 5 |
| Minor improvement | 4 |
| No change | 18 |
| Minor deterioration | 4 |
| Major deterioration | 0 |

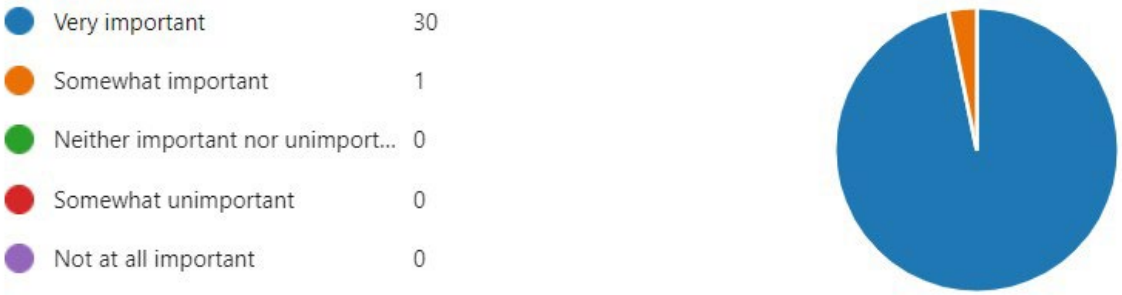


68) In response to your answers to Q51-67, if you would like to, please use your own words to provide further information below.

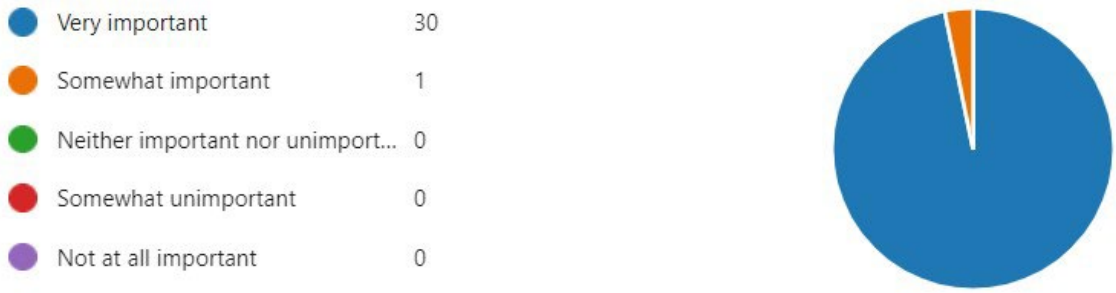
| | |
|---|---|
| 1 | Our son used to be unable to sleep, he is now able to sleep 12 hours a night without any need for any other medication other than the enzyme replacement infusions |
| 2 | We have not answered 51-53 as never had seizures |
| 3 | Our daughter has only ever had one seizure, this was before treatment started. Since starting treatment, she has not had any seizures. (Any types) We have had no problems with sleep. Our daughter now refuses to walk, her ability to walk happened at the same time her vision deteriorated. There was a massive difference in how our son and daughter lost the ability to walk. Our son lost his ability to walk over a few months prior to treatment. He was very clumsy, falling over his own feet, his balance was off and eventually he would only take a few steps at a time. Our daughter went from running around to being very reluctant to walk, she started to walk slowly feeling with her feet. Then one day she completely refused to walk and would just stand still. During this time she was losing her vision and became very upset, not understanding what was happening to her eyes. It is our belief that our daughter lost her ability to walk due to the loss of confidence when losing her vision. |
| 4 | We have seen a stabilisation of [redacted] condition and symptoms since starting treatment and with anti-epilepsy drugs. |
| 5 | No change listed due to not having issues previously with any area (pre-symptomatic child) |
| 6 | [redacted] began to show severe aggression prior to beginning Brineura. After approx 8 months of treatment, she was back to her old, very joyful self. Also, walking and communicating really improved around this time too. |
| 7 | [redacted] doesn't have "typical seizures" and can be very varied - however they are very well medically controlled. |
| 8 | There should be an option to elaborate on these answers. For example, my child cannot communicate verbally (talk) but she can most definitely make her needs known! Also, she experiences pain like many of us do for things like period pain. |
| 9 | Our child understands a lot of what we say to her and will even interject with her related opinion even if we're not talking to her! i.e "(Partner name), shall we have spaghetti for dinner?", Child answers, "Yeah!". Our child has been stable for 18 months with hardly any decline across the board of symptoms. |
| 10 | On overnight oxygen |
| 11 | We have noticed the more he does in a day on his feet and getting around can make his legs hurt more of a nighttime, so we now have medication for this! |
| 12 | 15 months seizure free. She only ever had one seizure in august 2022 |
| 13 | I've noticed major improvements since starting with the treatment, he's got so much better with everything, and we have not noticed any deterioration |
| 14 | All questions marked as no change are because we currently don't suffer from these symptoms. |
| 15 | Seizures are well controlled, mobility and swallowing slightly deteriorated in the first year as expected then stabilized, sleep is remarkably better, myoclonus is lot better, fatigue and tiredness is little better, some of that is due to the antiepileptics |
| 16 | Q49 - Regarding reaction to Brineura. After 24 infusions our daughter began having a reaction which was sickness & high temperature. She was given anti-sickness at the beginning for a further 6 infusions or so. She no longer gets that but continues to get a small dose of steroid. She had no further reaction since her initial reaction years ago. |

| | |
|---|---|
| 17 | A lot of the questions wasn't applicable for [redacted] she is very mobile, sleeps great, never noticed any pain etc only thing is we've not noticed any change in vision |
| 18 | Our son has been seizure free now (the seizures which would result in hospital admission/ambulance callout) for 23months aside from atonic seizures which were present for just a few months but are not longer present. |
| 19 | In regard to all of the above questions I have highlighted major improvements but I have to indicate that my child has never had to improve on most of these skills as he has not lost them. As sad as he has lost some, he does continue to learn new phrases and new names and has unbelievable memory and continues to thrive and very eager to learn and meet new people. |

69) In your opinion, how important is the benefit of the treatment with Brineura for the child/young person/younger adult in this survey on stabilisation of the disease?

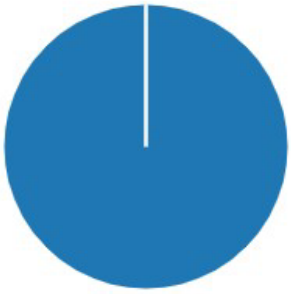



70) In your opinion, how important is the benefit of the treatment with Brineura for the child/young person/younger adult in this survey on activities of daily life?



71) In your opinion, how important is the benefit of the treatment with Brineura for the child/young person/younger adult in this survey on quality of life?

| | |
|---|---|
| Very important | 31 |
| Somewhat important | 0 |
| Neither important nor unimport... | 0 |
| Somewhat unimportant | 0 |
| Not at all important | 0 |



72) In your opinion, how important is the benefit of the treatment with Brineura for the child/young person/younger adult in this survey on leisure time?

| | |
|---|---|
| Very important | 29 |
| Somewhat important | 0 |
| Neither important nor unimport... | 2 |
| Somewhat unimportant | 0 |
| Not at all important | 0 |



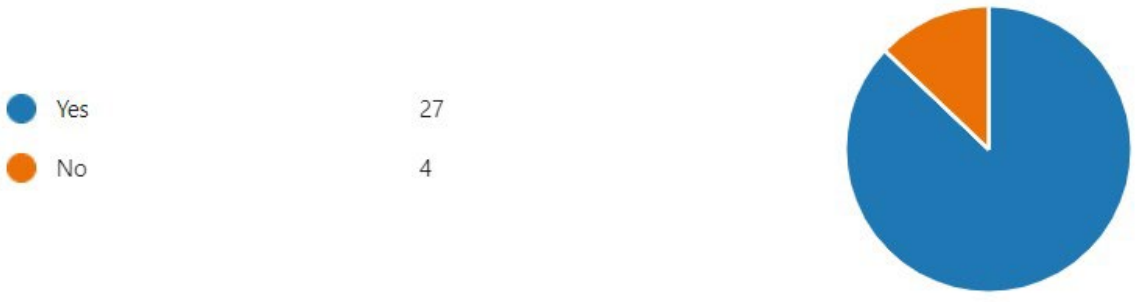
73) In your opinion, what are the other benefits of treatment with Brineura for the child/young person/younger adult in this survey?

| | |
|---|---|
| 1 | Without the treatment our daughter would be bed bound not able to walk talk or feed herself. Maybe she would have been blind or even dead. Thanks to treatment she can do all those things without struggling and she can enjoy her life. |
| 2 | Life expectancy for children with CNL2 Batten Disease is just 6-12 years. Our son will turn 13 in a couple of months. He still has a fantastic quality of life, because of this treatment he is still able to do many things that he enjoys in life including swimming and going aboard on holiday with his family. He is still able to show his emotions and can tell us through facial expressions when he is happy or sad. He smiles and laughs… especially if someone is doing something they are not supposed to which shows his understanding of the world around him. He loves to be outdoors and enjoys long walks and going to his big brothers' football matches. It is due to this treatment that our son isn't just alive, but he is still a very big part of our family, he is not bed bound instead he can join in with us as a family. |
| 3 | Critical in stopping further deterioration |
| 4 | It's halting the disease |

| | |
|---|---|
| 5 | The treatment has really stabilised his condition and he is thriving, very happy and enjoying an excellent quality of life. |
| 6 | Stabilisation of symptoms is a huge benefit to [redacted] and is all. Meaning she can continue to have a relatively normal life for a good period |
| 7 | As well as keeping children's skills and abilities for much longer the infusions also have a positive impact on their health. As siblings are often younger, they also become used to the infusions and the hospital environment a lot quicker and see this as just a normal part of their life…they do not know any different. |
| 8 | Treatment of Brineura has been given to my child prior to symptoms of Batten disease starting. This means that the treatment is stopping symptoms from beginning and enabling him to lead a normal life. |
| 9 | Not only is my child alive, but she also has an excellent quality of life. Without Brineura, I doubt she would be with us. And if she was, she'd be extremely ill, bed bound etc. |
| 10 | It gives the children more chance of staying how they are now than deteriorating even further, we have seen a change and without treatment would be in a worse position |
| 11 | Without the medication, [redacted] would have deteriorated so much more and at much higher rate. Therefore, Brineura is unparalleled in terms of importance in our lives, and we've move heaven and earth to attend treatments. It gives us time, quality of life, and skills for a longer time. |
| 12 | I believe that since my daughter has been on Brineura therapy, there have been major improvements in her day-to-day life, she is very happy, full of smiles for us constantly and she is very content as well as relaxed. The difference in her compared to a year ago prior to treatment is like night and day. We are very impressed with the results. |
| 13 | She is happy and content. She goes to school and enjoys her time there. She has friends. She smiles, she giggles. She has a big personality, and she is NOT READY TO GIVE UP! |
| 14 | To keep pain free, the more smiles and giggles the more I know how happy she is still |
| 15 | We won't notice our child forgetting things. I.E we saw Father Christmas a year ago and in the summer, she asked for the sweet she received while we were there. This past week she knew when asked "what does a cow/fish say?" which she hadn't done in a long while. Cognitively, our child is very strong. She jokes with us and others, finds things funny, learns new people's names and remembers them. Knows many family and friends' names and hasn't forgotten them. She is hugely social and empathetic. She understands when something she's watching is sad and can ask to skip it because t is sad. She picks up on our emotion when we are sad and will give us a hug. |
| 16 | I believe our child may not be alive without Brineura. Although we continue to see disease progression, it has slowed. Our child has a very good quality of life, I think Brineura helps with this a lot. |
| 17 | [redacted] is such a happy child; he loves spending time with his family and friends and without his treatment this wouldn't be possible. |
| 18 | Brineura is the sole reason that my child can still walk/run/climb/feed herself/ flick pages of her book etc, at 5 years old. All of these things benefit her quality of life greatly. |
| 19 | Brineura is giving our daughter a glimmer of hope to slow the onset of the disease. She did briefly start to walk on but now she can crawl and move about. Without it we are terrified of what life would be like. |
| 20 | Brineura has been intrumental in not only stabilizing the progression of the neurodegeneration in the brain but has also helped my child with mental development |

| | |
|---|---|
| | over the last few years. He has developed a good understanding and can follow simple instructions. He is stable from swallowing point of view and has not required a PEG so far, still managing orally. He is still mobile with support and walking frame and can engage in outdoor activities. He has good trunk control and can sit for reasonable periods, which has also helped us to travel abroad on holidays and to visit our family in India. Without Brineura, he may not have been with us by now or may have been bed bound requiring critical life support. |
| 21 | Our daughter has the most incredible quality of life. She enjoys ballet classes, she rides her scooter, she loves going on walks & collecting leaves and sticks in the woods with our dog. She loves climbing and going to adventure playgrounds. She loves arts and crafts, painting, drawing and one of her other favourite activities is playing with her dolls and real-life play. Due to attending hospital since she was a baby, she loves pretending to be a nurse. She tells everyone that she wants to be a nurse when she grows up. Her memory is amazing. Her chatting and interaction is amazing, she is emotionally intelligent and is so loving. The life she leads would simply not be possible without Brineura. She is all the proof you need to see Brineura works. Her eyesight is amazing and she is able, agile, mischievous and full of glorious energy and character. We are able to enjoy family adventures, holidays etc. We have a comparison with our older daughter who could not walk, had never spoken, was tube fed and had a multitude of health needs at the age of 8. |
| 22 | It gives her a life. She started a year before her brother, we can compare both children, if you met [redacted] you would never ever ever know she had the same condition as her brother. She doesn't need any aids to walk, she can walk an run just like a normal child, she says pretty much everything, she feeds herself, she can dress herself (in a fashion!) she is such a normal little girl who is now, touch wood, seizure free!!! She can do everything, she goes dancing, she loves swimming, the year made a massive Difference for her. This wouldn't have been the case without this treatment. |
| 23 | Each option is very important, we want our son to experience everything he can in life and be happy. |
| 24 | Child is living a great life under the circumstances. He enjoys school, family and carers and has a great sense of humour. He is able to communicate all his needs and he has many friends in the community. None of this would be possible without the treatment (as he would not survive and deteriorate quickly without Brineura). |

74) In your opinion, do you think the frequency of treatment is sufficient to manage disease progression?

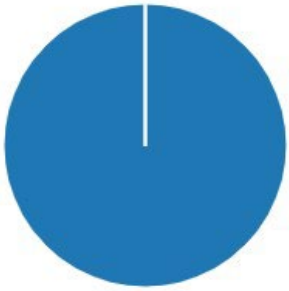


75) Are there any aspects of the CLN2 Batten disease that Brineura cannot help with (please give details below)?

| | |
|---|---|
| 1 | Brineura gave our daughter life. |
| 2 | Brineura does not help with the loss of vision. |
| 3 | Infusions unlikely to recover lost skills and unable to affect deterioration in eyes. |
| 4 | Sight. |
| 5 | Sleeping or lack of which is a huge issue and has a huge impact on all the family. |
| 6 | Deterioration of vision. |
| 7 | Vision loss. |
| 8 | Vision loss. |
| 9 | Saving vision, stopping seizures/myoclonus. |
| 10 | It can't reverse what has already deteriorated due to when the children are put on the treatment. |
| 11 | Eyesight. It's doesn't stop the regression. It doesn't give back what is lost. |
| 12 | Vision loss and reversal of the disease effects. |
| 13 | We are all under the understanding that this treatment is not a cure but slows the disease down and it is down to the child when they are ready to give up. |
| 14 | Eyesight. Her eyes cannot see no more. |
| 15 | I would be interested to see the impact on disease progression with increase of frequency of treatment, especially within the first year of treatment. I wonder whether our child may still be walking if this was the case, we noticed a stark change in our child within the first year after the fortnightly treatment and felt she was ready for the next dose within 7-10 days. Stability, energy levels and language particularly would be noticeably and positively affected. Teachers, friends and family still comment on it now as our child is more tired in the few days leading up to treatment. We are aware that Brieura is not supposed to help with maintaining eyesight. |
| 16 | Sight loss. We continue to see slow general disease progression. |
| 17 | Vision loss Epilepsy (stop seizures all together). |
| 18 | Vision. |
| 19 | Eyesight. |
| 20 | Treatment for the loss of vision. |
| 21 | Losing her sight. |
| 22 | Certainly Brineura is not controlling the progression of degenerative retinopathy as it is not reaching the eyes, which is a major issue, but this was always known that it will not help with that, hence GOSH conducted the off label trial of Brineura in the eyes via intravitreal injections and it has shown some promising results in some of the children. |
| 23 | We have always understood that seizures and vision loss were not part of the treatment benefits. |
| 24 | Sightloss. I remember being told the children couldn't have the treatment more that every 2 weeks but if it was possible to have more than I'd say yes. |
| 25 | Sadly my child has lost vision he does continue to independently try to get about and I feel as many do that some sort of sight as he continues to see light and dark, recognise family and friends and still watches ipad. |
| 26 | Vision deterioration/blindness. |

76) Were you made aware of this before starting treatment?

| | |
|---|---|
| Yes | 26 |
| No | 0 |



77) In your opinion, what do you think is the most difficult aspect of your child/young person/younger adult 's treatment with Brineura?

| | |
|---|---|
| 1 | Every 6-12 testing. We believe that EEG, ECG, MRI, psychology testing unnecessary. Doctors should just see how our daughter is doing comparing to children without treatment. |
| 2 | Before we moved centres to one closer to home, we would have said travelling for treatment. Now the most difficult aspect is juggling family life around a treatment which is every two weeks on the same day at the same time. However, this is minor and something that we cope with thanks to the support of family and friends. |
| 3 | Impact of requiring a full day for treatment every fortnight and that treatment will be required indefinitely. |
| 4 | Don't think there is one |
| 5 | The long time for the infusion to take place. |
| 6 | Giving medication to sedate or for epilepsy is very hard with [redacted]. |
| 7 | Vision loss. |
| 8 | Time spent during the infusion, but this isn't an issue to me as I know how important it is. |
| 9 | The refusal of NICE to initially allow [redacted] access to treatment. We should not have had to fight for months for it, watching her deteriorating. She lost skills that she never fully regained. Now it is the whole NICE process. It is extremely stressful, similar to living on a knife edge, whilst they plot their next penny-pinching move to use my child as a commodity to drive price down. |
| 10 | Nothing it is all worth it |
| 11 | The regular testing that you have to put your child through as part of the MAA. The eyesight testing is particularly gruelling - especially as there is nothing that can be done to even slow the regression. In fact, the only major seizures [redacted] has endured have been triggered as a result of electrophysiology tests. We now monitor and cease tests if we feel this is too triggering. |
| 12 | None. |
| 13 | Nothing. It is keeping her alive and she is HAPPY to be here. |
| 14 | Keeping her still for the 4 hours 12 mins 😜 |

| | |
|---|---|
| 15 | The fear of the device failing and not getting the full amount of the coveted drug. During infusion, keeping an eye on the child to make sure the accessed needle is not knocked out by my active child! |
| 16 | Seeing continued deterioration. |
| 17 | Sometimes [redacted] can become frustrated with long periods of time in hospital and appointments. |
| 18 | The infusion days are tiring. |
| 19 | He does have any difficulty |
| 20 | The initial brain surgery. |
| 21 | The long day, pre-treatment check-ups and receiving her sedation meds. |
| 22 | In my opinion it's the frequency of the treatment with all day being in hospital every fortnight, missing out the school and also as a family it does have a major impact on our second child as we are not able to give him the same attention due to the volume of hospital visits and care required. |
| 23 | Nothing. Our daughter is very comfortable with hospitals and needles as it is all she has known so we don't feel there are any difficulties from our personal point of view. |
| 24 | Some of the assessments aren't really necessary. |
| 25 | The extra testing that goes alongside it, particularly the psychology testing and the questionnaire. The psychology test does not show what our son is capable of, it is performed in an unfamiliar setting with strangers, with toys that he wouldn't usually play with. It is hard for us as parent to put our son through these tests knowing they just frustrate him. I don't feel our son's quality of life should be judged on a questionnaire that is so open to interpretation. With regards to the treatment and the day itself, we do not find it difficult, our son is happy enough, eats well, copes very well with being prodded and poked by the nurses. He makes the 'job' of going through this easy as he is so good. |
| 26 | My child hasn't got an issue receiving Brineura, he is very used to it after 9 years, he has never suffered or had an issue being in hospital. |
| 27 | By far the most difficult aspect is the stress of the possibility that his treatment might go away. We have moved countries multiple times to make sure we never found ourselves in a situation where he would be without treatment as this would have devastating consequences. It is obviously difficult dealing with the eternal logistics of his bi-weekly treatment which makes, say, planning travel and work very difficult. But it is a small price to pay. |

78) Please use your own words to describe positive or negative aspects of treatment with Brineura and its impact on the child/young person/younger adult in this survey.

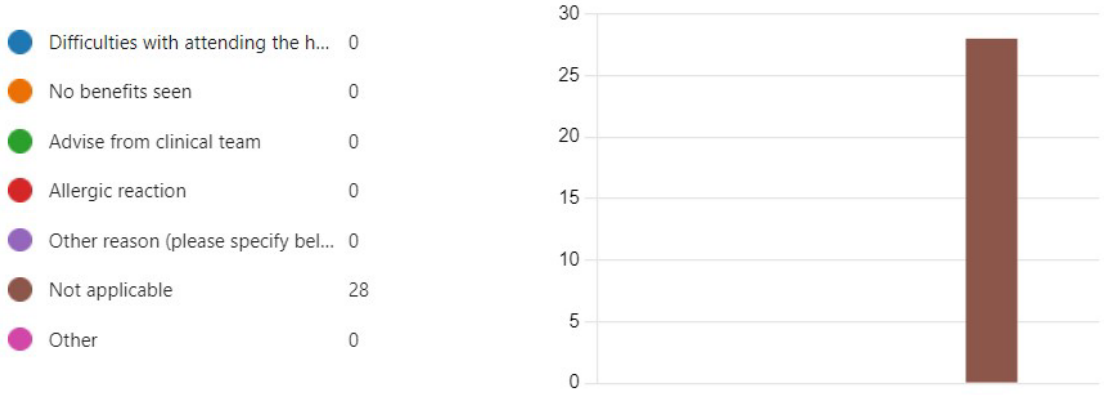
| | |
|---|---|
| 1 | We can only see positive aspects. She started walking again 3 months after starting treatment. She can speak and learning new words. She retains memory. She can remember recent things or that happened some time ago |
| 2 | Brineura slows down the progression of Batten disease, it improves quality of life and reduces the amount of seizures and pain a child with CNL2 Batten Disease experiences. A child who receives treatment with less symptoms of the disease seems to stay healthy for longer and the progression is slowed down even more. For our son, seizures have improved massively, going from many daily tonic clonic seizures to one maybe two tonic |

| | |
|---|---|
| | clonic seizure per year. Absence seizure which used to happen pretty much all day now do not happen at all and have been nonexistent for years. Our son is more alert, settled and happy, he is able to enjoy family life and take part in activities and holidays aboard, something that would not be possible without enzyme replacement therapy. His quality of life has been massively improved. On average he has one hospital admission per year which range from one overnight to 5 nights compared to the monthly stays in hospital before treatment. |
| 3 | Positive impact is prevention of deterioration. Negative impact of attending for treatment is far outweighed by the positive. |
| 4 | The positive aspects include the stabilisation of his disease progression, he is very healthy and happy and has a great quality of life. The negatives are when the infusions have not gone well, e.g. his very first port (not in the UK) protruded, and he became very ill with meningitis The replacement port put in was not put in correctly and so he had to have a 3rd op to remove it and out in a new port. |
| 5 | It's difficult as we are in a fairly good routine 6 months in but we know we will see a decline at some point. Hard not knowing what aspects are working and which are not as [redacted] cannot tell us. |
| 6 | Before we moved centres to one closer to home, we would of said travelling for treatment. Now the most difficult aspect is juggling family life around a treatment which is every two weeks on the same day at the same time. However, this is minor and something that we cope with thanks to the support of family and friends. |
| 7 | Brineura is enabling my son to lead a normal life and remain pre-symptomatic. There are no negative aspects to him receiving treatment. |
| 8 | pos: slow down disease, neg: infusion every 2 weeks, time of infusion. |
| 9 | [redacted] completely takes the treatment in her stride. She's happy on infusion days. The nurses are so nice, I think she enjoys it in a way. I'm happy as I feel safe there; the team are so conscientious and caring. |
| 10 | It has made a drastic improvement since being on treatment, seizures are more controlled, child more alert. |
| 11 | The treatment has definitely shown extremely positive results, not only we have noticed but many health professionals at multiple hospitals have commented on how well my daughter has been doing since the start of treatment. |
| 12 | Positive - keeping her alive. Part of her everyday life as we have been on it for 10 years Negatives - the possibility that her shunt could get infected. |
| 13 | No negatives. Most positive is that her smiles and giggles we still have. 7 years of treatment and she's so happy and pain free. |
| 14 | We would never be without this drug as it is giving us our child her best possible quality of life for as long as possible. It is without a doubt, extending her life and keeping her well. Initially the commitment to a fortnightly infusion felt weighty and scary but now it is part of our normal life pattern. |
| 15 | We feel the positive aspects for our child is he's able to go to school and socialise with his friends, he's always happy when he's socialising with people, he's able to use the equipment provided for him for better quality of life. The only negative aspect is the amount time in hospital for [redacted]. |
| 16 | The tiring infusion days are more than worth the benefits that Brineura brings to my child. She is familiar with the infusion routine now and actually enjoys watching her iPad |

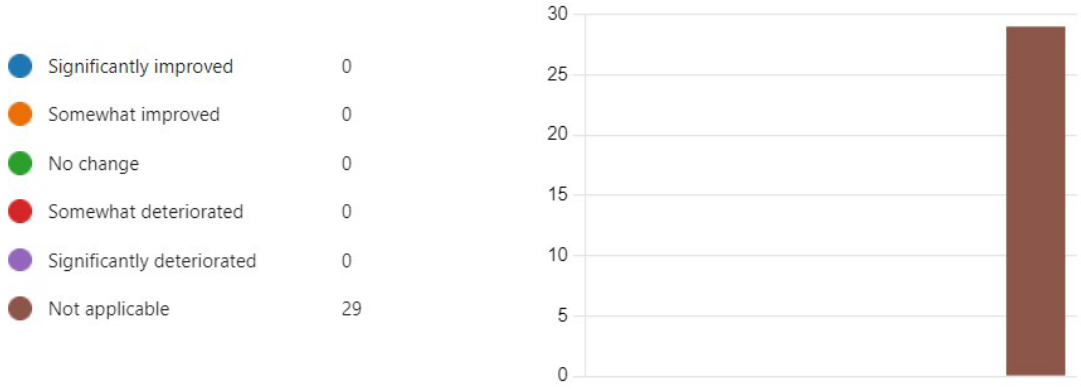
| | |
|---|---|
| | all day. Brineura gives my daughter a great quality of life still and she has not really lost any skills since starting 2 years ago. |
| 17 | I think the treatment is all positive only thing that is negative that the treatment could stop |
| 18 | After 6 months of treatment we are slowly starting to see improvements in our child's life. We are noticing less seizures and overall, his speech and balance / stability does seem to be getting better. He is more aware and responds to more. |
| 19 | [redacted] does not like to be touched and finds the check-ups very distressing as well as the receiving of the medication beforehand. However, she does recover very quickly. We find the nil by mouth tricky too. |
| 20 | Brineura has been instrumental in not only stabilizing the progression of the neurodegeneration in the brain but has also helped my child with mental development over the last few years. He has developed a good understanding and can follow simple instructions. He is stable from swallowing point of view and has not required a PEG so far, still managing orally. He is still mobile with support and walking frame and can engage in outdoor activities. He has good trunk control and can sit for reasonable periods, which has also helped us to travel abroad on holidays and to visit our family in India. Without Brineura, he may not have been with us by now or may have been bed bound requiring critical life support. Seizures are well controlled, Mobility and swallowing slightly deteriorated in the first year as expected then stabilized, sleep is remarkably better, myoclonus is lot better, fatigue and tiredness is little better, some of that is due to the antiepileptics Certainly Brineura is not controlling the progression of degenerative retinopathy as it is not reaching the eyes, which is a major issue, but this was always known that it will not help with that, hence GOSH conducted the off label trial of Brineura in the eyes via intravitreal injections and it has shown some promising results in some of the children. |
| 21 | The most obvious positive being the delay in disease progression, he is still walking, talking, eating and drinking which, looking at natural history, I don't believe would be possible without Brineura. His cognitive abilities are still wonderful, he is still great at socialising and loves other children Families are being brought together We get to keep our son for longer! Aside from him having battens in the first place and having to go through brain surgery. This treatment is prolonging my child's life so I struggle to find a negative. |
| | The negative is that my child has this condition firstly. I can't say I'm negative with the treatment my child receives, as a mother after 9 years I've known the treatment will only prolong life. I always think if cost wasn't an issue and as the child gets older, they receive more drugs as its obvious child as get older are slow declining but still I feel the child mental functions are still very strong and the body isnt getting the help it needs as the child body gets bigger. Knowing that won't happen, my child is 12 can't see still slightly, can crawl alone, sings, plays with toys, goes swimming, goes the funfair, eats a full varied blended oral diet as well as eating a variety of crisps. Has emotions, love to kiss and cuddle anyone who he loves, plays with his big dog. Goes the high school ear 8 and has friends and relationships with children and adults of all ages. I have no negatives about the treatment my child receives. |
| | Thanks to the treatment with Brineura, I believe the illness has slowed down. |

| | |
|---|---|
| | Brineura not only keeps child alive, it also halts the deterioration. It is very clear to us that without just one or two treatments he would decline significantly. He is a very happy child and able to do most things. He enjoys good food, music, stories and shows. He loves riding the bus. He can feed himself and can help get dressed and undressed. He is rarely unhappy or sad. He was one of the first children on the clinical trial and we consider ourselves very lucky that we were able to get him in treatment before it was too late. We see no negative aspects regarding the treatment itself. GOSH have been no less than amazing and supportive, professional. One negative aspect of brain infusions is the port that is embedded in his head which occasionally needs changing which is a bit of an unpleasant event. |

79) If the child/young person/younger adult in this survey discontinued receiving Brineura, why was that decision taken?



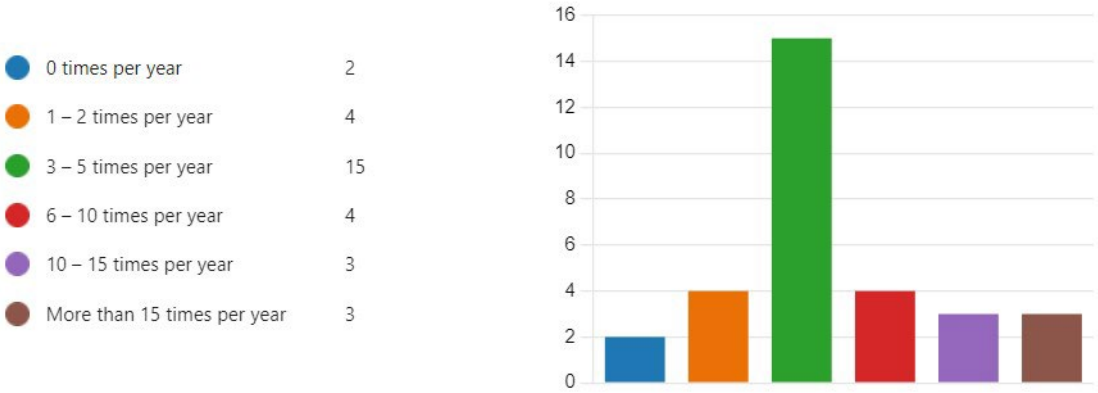

80) If the child/young person/younger adult in this survey discontinued receiving Brineura, have you noticed any change in their condition?



81) In response to your answers to Q79-80, if you would like to, please use your own words to provide further information below.

N/A

82) Apart from infusion days, how often do you need to visit a hospital?

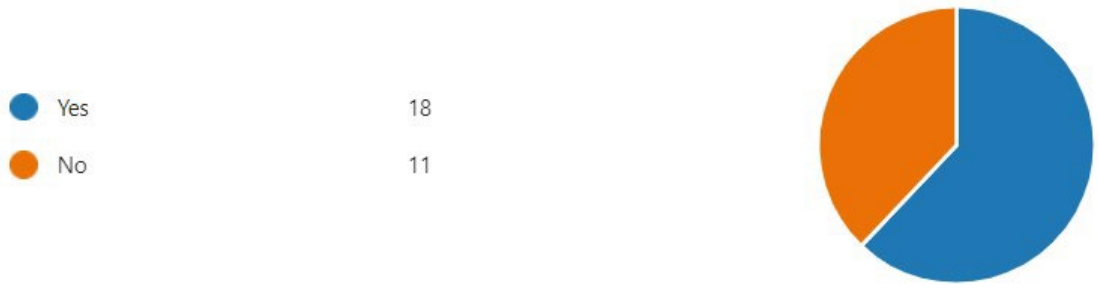



83) What are the purposes of these additional hospital visits (please specify below)?

| | |
|---|---|
| 1 | MAA additional testing like ECG MRI, and eye treatment. |
| 2 | Extra appointments mainly to do with the Managed Access Agreement that cannot be fitted in on the same day as infusions. For example, MRI scans. |
| 3 | Managed Access Agreement test / review requirements. |
| 4 | Epilepsy/psychology appointments. |
| 5 | Orthotics and cardiac due to his congenital heart condition (not related to batten disease). |
| 6 | Eyesight tests. Psychology appointments. CT scans. Paediatric appointments. |
| 7 | Managed Access Agreement appointments. Vision related appointments (not related to Batten disease) |
| 8 | control check |
| 9 | MAA hoop jumping assessments. Annual local neurologist appointment. Usual childhood ailments, urine/throat/chest infections. |
| 10 | Treatment review, physio appointments, treatment in Great Ormond Street. |
| 11 | Various other symptom appointments, symptom related treatments, MAA tests, medical reviews, epilepsy related seizures. |
| 12 | Eyesight appointments, physio, Regenxbio trial visits to GOSH in London and Brineura reviews. |
| 13 | When hospital admission required due to illness (cough/cold/infection) we have been lucky. |
| 14 | MRI scans spine X-rays. |
| 15 | Largely MAA hospitals appointments. A lot of previous face to face appointments have been moved to phone calls or video calls which is helpful. We have access to three hospitals. Our local hospital in [redacted], neurology in [redacted] and [redacted] for infusions and MAA assessments. |

| | |
|---|---|
| 16 | To see many different professionals involved in care, also managed access agreement appointments. |
| 17 | MAA assessments. |
| 18 | MRI scans Ophthalmology Follow up appointment (metabolic team) Paediatrician appointments (monthly) EEG scan ECG scan Physio appointments Dietician Wheelchair services. |
| 19 | MAA Assessments Neurology appointments. |
| 20 | Checkups in line with our MAA. |
| 21 | Epilepsy check-ups, eye tests. |
| 22 | To attend Neurology clinics, Cardiology clinics, Ophthalmology clinics, Spine clinics, Dental appointments, Orthotics appointments. |
| 23 | Check-ups most probably. |
| 24 | Eye tests (child is short sighted so has extra eye tests) ECG'S Neurology Paediatrician Testing for MAA. |
| 25 | Additional appointments for the MAA. |
| 26 | Neurology, Paediatrician and Optician. |

84) Are these visits to different hospitals than the one you visit for infusions?




85) As a carer, what do you want most from any treatment for CLN2 Batten disease?

| | |
|---|---|
| 1 | I'd like treatment to be accessible in town where we live or closest city. I have to take time off work to come for treatment. If it was in our hometown only one of parents could attend treatment. Otherwise with long distance we both have to go due to difficulty in care. |
| 2 | A cure, that is a onetime treatment that can reverse any damage that has already taken place. |
| 3 | Stabilisation to allow longer lifetime and quality of life to remain. |
| 4 | To halt the disease. |
| 5 | To benefit my child's health and happiness. |
| 6 | Support from specialists and other parents as it's so rare it's the only way to really understand the disease. Stabilising of symptoms to make the most of limited time with [redacted]. |

| | |
|---|---|
| 7 | For a cure, for our children to be able to receive a treatment which will reverse any damage already made. |
| 8 | For it to continue until there is a cure. |
| 9 | to stop disease completely |
| 10 | Security of treatment. For the treatment to stabilise or improve [redacted] quality of life. To keep her pain free and comfortable Initially I wanted it to stabilise the disease until there was a cure. I think that is an unrealistic expectation given the current climate. More than anything, I just want [redacted] to live a good life, for as long as possible. |
| 11 | Prolonging life of child. |
| 12 | Competent staff with compassion and a friendly smile who call us on 1st name basis rather than "Are you Mum/Dad". |
| | I would love for the treatment to be able to reverse the disease completely, but I totally understand that this is not a possibility currently. |
| | To keep my daughter as well as possible and alive. |
| | That one big cure for our future children. |
| | I am always hoping for a cure but in the absence of that, a treatment which helps my child live well, which Brineura does. |
| | A cure. |
| | To give our baby's the best chance at life and a good quality of life to! |
| | A cure. |
| | Delay or stop regression. Prevent pain. Maintain quality of life. |
| | A cure. |
| | We want our boy to be able to enjoy his best life. He laughs and smiles and we never want him to lose this. |
| | To slow down the effects of the disease and give [redacted] a good quality of life. |
| | To keep my child stable, seizure free, continue to grow physically mentally and intellectually, continue to eat, and drink normally, remain pain free and hopefully develop some form of speech in future. |
| | As a carer it gives us more time as a family and gives the child and family time to enjoy life. |
| | To save my sons life. |
| | To make life easy as possible for the child and continue treatment. |
| | I've observed that the illness has slowed down. |
| | I want my son to live a good life. He is happy, verbal, expresses his love with words, sings, laughs. He is a happy peanut with the more love and strength to give than you could possibly imagine. He would not be alive without Brineura. |

86) After considering all the available treatments, in your opinion are there any unmet needs for patients with CLN2 Batten disease?

| | |
|---|---|
| 1 | I'm not aware of any other available treatments. |
| 2 | Not at our treatment centre. |
| 3 | Clearly the potential for a single treatment therapy would make a huge difference in avoiding the need for indefinite fortnightly treatment. In future, any method of repairing already damaged cells. |
| 4 | A cure. |

| | |
|---|---|
| 5 | No not really. We are really well supported with access to all the specialists we need. |
| 6 | The link between vision loss and mobility loss. Also, the psychology assessments are not fit for purpose for those children with vision loss. For example, a child with full vision may be able to recognise colours and letters. When this child vision deteriorates the assessments will show that this child can no longer recognise the same colours and letters as they could at their last assessment. This child will lose points on the rating scale. However, the reason they can no longer recognise the colours and letters is due to the loss of vision not loss of skills. |
| 7 | Gene therapy for vision loss and an overall central nervous system cure |
| 8 | Yes, the cure for CLN2. The cure or stabilisation for vision loss. |
| 9 | there are no other treatments |
| 10 | Eyesight treatments should be more available for patients due to the rapid decline children suffer in losing their eyesight. |
| 11 | Yes, as there is no cure!! |
| 12 | Opportunities to access eyesight treatment. |
| 13 | Yes, we don't have a cure |
| 14 | Yes regenxbio |
| 15 | Seems like a postcode lottery in terms of local services. The entitlement to a treatment like Brineura that is keeping my daughter alive and healthy should not be questioned. |
| 16 | Yes, the trail one what came out this year but then decided not to carry it on cause off the money situation |
| 17 | Treatment on the eyes via ERT should be standard as part of the MAA. It should be administered at the same time as their brain infusion. |
| 18 | There is no other treatment apart from Brineura. Despite the fact that it does not stop the progression of blindness, it is still helping immensely to give my child a reasonable quality of life and keep him stable and happy. |
| 19 | There is no other treatment available for CLN2. So, this is our child's only chance to live a healthy life. |
| 20 | Funding for more equipment, more physiotherapy advice or parents on how they can help their child at home. Keeping their strength is so important Understanding from local professionals of what battens is. |
| 21 | no |
| 22 | I can't think of any… |
| 23 | No, aside for treatment for the loss of eyesight, which is being trialled. |

**PART 5**

**Services**

87) Has the child/young person/younger adult in this survey required the use of a physiotherapist?

| | |
|---|---|
| No | 5 |
| Yes, still using | 26 |
| Yes, no longer using | 0 |



88) Has the child/young person/younger adult in this survey required the use of an occupational therapist?

| | |
|---|---|
| No | 4 |
| Yes, still using | 27 |
| Yes, no longer using | 0 |



89) Has the child/young person/younger adult in this survey required the use of a speech therapist?

| | |
|---|---|
| No | 1 |
| Yes, still using | 20 |
| Yes, no longer using | 10 |



90) Has the child/young person/younger adult in this survey required the use of a dietician?

| | |
|---|---|
| No | 15 |
| Yes, still using | 16 |
| Yes, no longer using | 0 |



91) Due to the child/young person/younger adult in this survey having CLN2, have you ever needed mental health services?

| | |
|---|---|
| Yes | 9 |
| No | 22 |



92) Due to the child/young person/younger adult in this survey having CLN2, have you ever needed social care?

| | |
|---|---|
| Yes | 12 |
| No | 19 |



93) Due to the child/young person/younger adult in this survey having CLN2, have you ever needed benefits or financial support?

| | |
|---|---|
| Yes | 26 |
| No | 5 |



94) Due to the child/young person/younger adult in this survey having CLN2, have you ever needed home adaptations?

| | |
|---|---|
| Yes | 20 |
| No | 10 |



95) Due to the child/young person/younger adult in this survey having CLN2, have you ever needed specialised vehicles?

| | |
|---|---|
| Yes | 10 |
| No | 21 |



96) Due to the child/young person/younger adult in this survey having CLN2, have they ever needed time off school (child/young person/younger adult in this survey)?

| | |
|---|---|
| Yes | 25 |
| No | 6 |



97) Due to the child/young person/younger adult in this survey having CLN2, have you ever needed time off work?

| | |
|---|---|
| Yes | 22 |
| No | 9 |

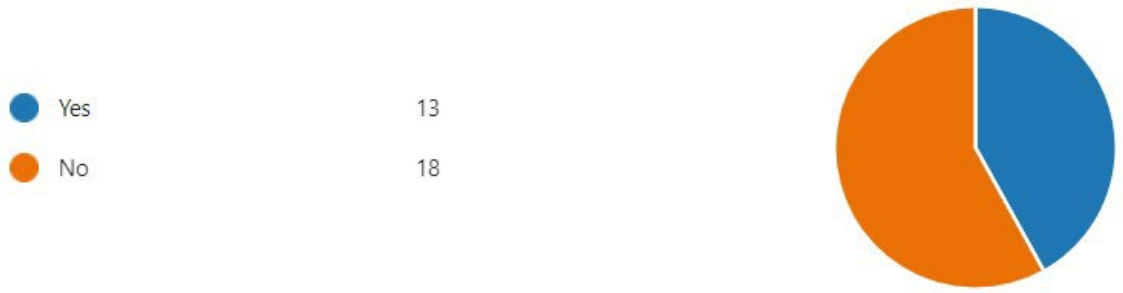


98) Due to the child/young person/younger adult in this survey having CLN2, have you ever needed a personal assistant?

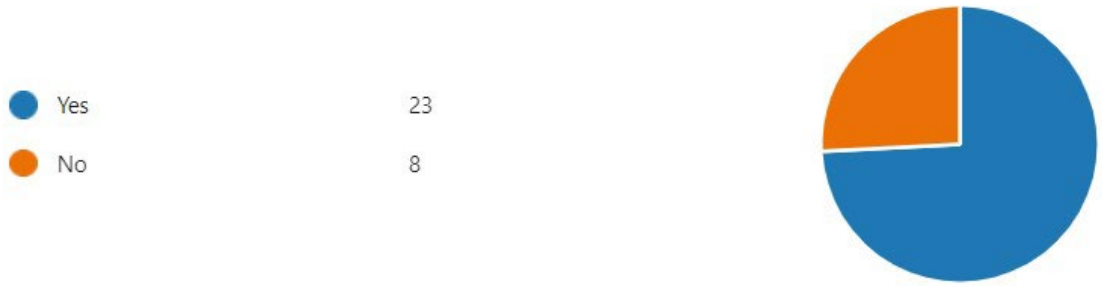
| | |
|---|---|
| Yes | 12 |
| No | 19 |



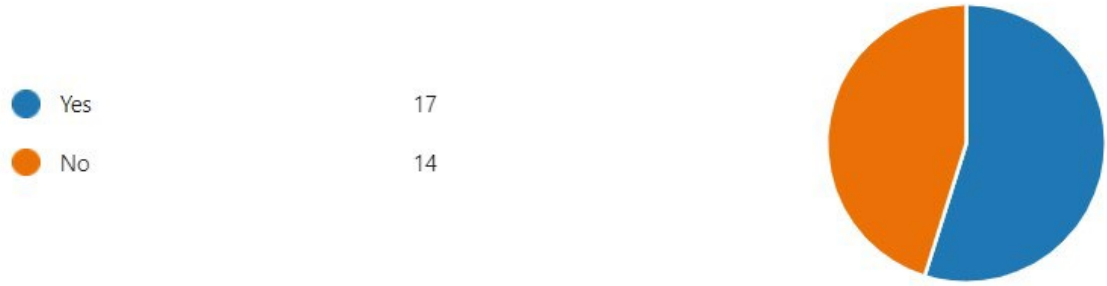
99) Due to the child/young person/younger adult in this survey having CLN2, have they ever needed adaptations at a mainstream school/college?




100) Due to the child/young person/younger adult in this survey having CLN2, have they ever needed to attend a specialist school?




101) Was it difficult to get any of the services in Q87-Q100?




102) How long did it take for you to get these services?

| | |
|---|---|
| 1 | We were very lucky and got referred to all services shortly after diagnosis |
| 2 | At the start of this journey in 2015 it was very hard to get these services in place due to our son being very well at the time of diagnosis. Professionals did not believe he needed additional services whereas we believed these should be in place for as and when he |

| | |
|---|---|
| | needed them. As our son was diagnosed before a treatment was available his symptoms appeared very quickly, and we would often find that by the time he made his way to the front of a waiting list for a piece of equipment his skills would have changed and he would no longer be in need of that piece of equipment but instead would need something different. He would then be added to another waiting list and the cycle continued. |
| 3 | Adaptations - 3 years. Financial support - 6 months |
| 4 | Quite quickly. |
| 5 | Still awaiting specialist school. Really difficult getting a EHCP and looks like we'll be a year later for school. |
| 6 | Services were already involved for our son so when our daughter needed them, she was added to their services. |
| 7 | Couple months |
| 8 | They are in house at [redacted] specialist school |
| 9 | We are still awaiting due to the child being under a different county when staying with her mum and we don't have access to the same things in our county, we had to fundraise to be able to get a disability pram but don't have any other equipment |
| 10 | our local council decided to cut paid carer hours because I was giving up work to become a carer. They stated that I and [redacted] were all the care [redacted] needed. After a severe mental health episode, they reinstated paid carer hours. |
| 11 | Due to living in a different county from my daughter we have struggled to get any support for equipment, specialised vehicle and financial support as this all goes to my daughter's mother who does not share equipment with myself and partner when we pick up and care for my daughter. |
| 12 | This is difficult to answer as our journey has been over a long time (10 years). I feel that I have had to fight the system to get the support my daughter needs. I know other families have experienced the same. |
| 13 | Largely, we have been very well and urgently supported. Adaptations to our home was probably the most frustrating service due to initial poor management and illogical processes. Yet we have been thankful for the outcomes. |
| 14 | Took around a year to get [redacted] into a specialist school due to lack of funding |
| 15 | Once we knew exactly what [redacted] needs were, the services were available quite quickly. |
| 16 | It took us years to get the team that we have now. |
| 17 | Some was very quick but getting rehoused took over a year. |
| 18 | 6-12 months. |
| 19 | We are currently going through home adaptations and waiting for a specialist school place to become available. |
| 20 | Social services and Social Occupational therapy always take a few weeks to months, but rest are quick in our area to respond. |
| 21 | Was difficult to get her into a SEND school due to funding. |
| 22 | They were available at our son's school so he has been seen quite quickly. |
| 23 | A few weeks to a few months. |
| 24 | Sometimes it has been several months or even a year… |
| 25 | Within months. |
| 26 | Year's overall |

103) Who paid for these services?

| | |
|---|---|
| 1 | NHS provided or council |
| 2 | Our local authority |
| 3 | Adaptations - Local Authority |
| 4 | Local authority. |
| | |
| 5 | Local authorities |
| 6 | The local authority |
| 7 | NHS |
| 8 | I occasionally pay for private physio services |
| 9 | Myself and her dad |
| 10 | Council: SALT, Physio, School services, dietician, Private: Vehicle, Shared Council and Private: Housing adaptations, Physio, SALT |
| 11 | My partner's workplace did fundraising to buy us a specialised pram as this is the only equipment we were able to get due to the issues with the NHS support. |
| 12 | Health & Social care |
| 13 | The local council has paid the majority and we have put in about 10%. |
| 14 | Some NHS funded some private |
| 15 | Local authority. |
| 16 | Council |
| 17 | Local authority, NHS |
| 18 | through the council |
| 19 | NHS Us (parent) |
| 20 | NHS |
| 21 | Ourselves for the most part and Hackney Council |

104) In response to your answers to Q87 - Q103, if you would like to, please use your own words to provide further information below.

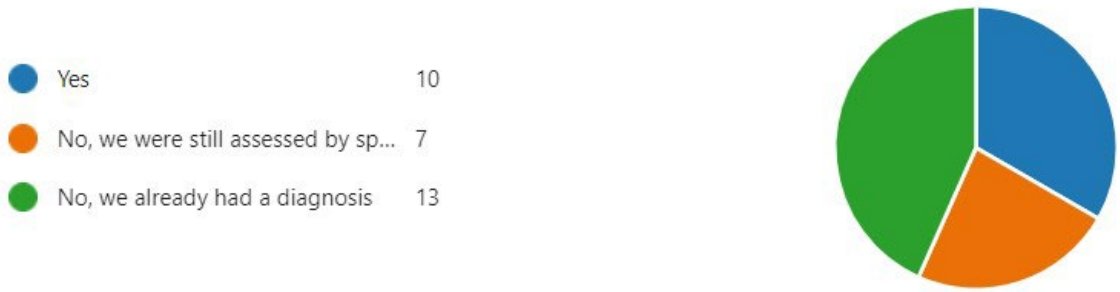
| | |
|---|---|
| 1 | We removed our son from mainstream school as they were unable to meet his needs. Unfortunately, they would not admit to this and instead carried on receiving our sons school funding. It was very hard for us to then trust anyone with our son so out of choice we decided to home school him. Thankfully now 6 years on with have an amazing outreach team who come to our home from a special school to teach him and do physiotherapy within the comfort of his own home three times a week. |
| 2 | We also accessed some private services e.g. brainwave in our attempt to get a diagnosis. |
| 3 | We are very fortunate our local authorities are very supportive and well-funded to support. |
| 4 | We're very lucky as our community and school services are excellent |
| 5 | In Jan 2024, we will get our 7th different social worker since Sept 2020 - the amount of professionals involved is incredible. Parents may try to carry on working, but in order to gain any work/life balance it becomes necessary to give up work. |
| 6 | very rarely misses school - only for treatment and health and therapy appointments |
| 7 | It's a postcode lottery for local services. Brineura should come hand in hand with a metabolic trained physio to keep the children strong. |

| | |
|---|---|
| 8 | It has been a constant fight to get our child the help he needed. Our local authority and school board didn't really know what Battens Disease was and it took much longer than needed to get things organized and in place. |
| 9 | My child attended mainstream school only for a year in Nursery, from reception onwards he has been in a Special needs school |
| 10 | no matter what services are involved or time of work or having to leave work due to infusions these are essential and are allowing us more time with our daughter and brineura is keeping our daughter alive |
| 11 | Us as parents have funded speech therapy as NHS we very slow to help and didn't seem to want to. All other therapies have been available through our son's school and have been amazing. We have had home adaptions to help make our home safer but have also paid towards these as the local authority would not cover some of the costs. For example, the flooring. We have personally funded AFO's and specialised shoes as NHS ones were not helpful |
| 12 | Child is in [redacted] school in London. He has had a few things paid for, such as wheelchair etc. We have some money coming in to help support paying for a full-time carer as we both work full time. |

**PART 6**

**Impact of COVID**

105) Do you feel that the COVID pandemic caused a delay in getting a CLN2 diagnosis for the child/young person/younger adult in this survey?



106) If you were already accessing mental health services, was it affected during the COVID-19 pandemic?

| | |
|---|---|
| Yes | 4 |
| No | 21 |



107) If you were already accessing medication, was the supply affected during the COVID-19 pandemic?

| | |
|---|---|
| Yes | 5 |
| No | 22 |



108) If you were already accessing medication, was the supply affected during the COVID-19 pandemic?

| | |
|---|---|
| Yes | 16 |
| No | 10 |



109) If you were already accessing physiotherapy, was it affected during the COVID-19 pandemic?

| | |
|---|---|
| Yes | 13 |
| No | 14 |



110) If you were already accessing occupational therapy, was it affected during the COVID-19 pandemic?

| | |
|---|---|
| Yes | 12 |
| No | 15 |



111) If you were already accessing sensory therapy, was it affected during the COVID-19 pandemic?

| | |
|---|---|
| Yes | 6 |
| No | 18 |



112) Was schooling affected during the COVID-19 pandemic?

| | |
|---|---|
| Yes | 25 |
| No | 4 |



113) Were there any other services that you already had access to that were affected during the COVID-19 pandemic (please specify the service)?

| | |
|---|---|
| Yes | 9 |
| No | 19 |
| Option 3 | 0 |



114) If you were referred to any of the following services, mental health, medication, speech and language therapy, physiotherapy, occupational therapy, sensory therapy, schooling, or other service, do you feel the COVID-19 pandemic caused a delay in getting access?

| | |
|---|---|
| Yes | 19 |
| No | 8 |



115) Which of the services in Q114 do you feel were delayed by the COVID-19 pandemic?

| | |
|---|---|
| 1 | Hydrotherapy, home adaptations |
| 2 | We found it extremely difficult to see a GP during the pandemic |
| 3 | Non - no issue accessing limited services that were required |
| 4 | MRI scan, EGG, Genetics tests |
| 5 | VI specialists |
| 6 | Preschools, sure start program for 2-3 years old |
| 7 | All of them. It also delayed the start of [redacted] moving from mainstream to specialist school |
| 8 | MRI testing |
| 9 | Speech and language |
| 10 | all services were affected due to lockdown and the pandemic |
| 11 | School OT physiotherapist |
| 12 | Our child's first major seizure was in May 2020 when she was 4. They said due to protocol with regard to COVID it was going to be impossible to let her have an MRI. Those services had been paused and they saw it as non-urgent. This changed within two months as seizures increased and we repeatedly landed in hospital. Once we blue lighted to the specialist hospital in [redacted] there were no problems accessing MRI. In three months however, she had changed a lot and symptoms were coming thick and fast. |
| 13 | Physiotherapy, language therapy, schooling & sensory therapy. |
| 14 | All of them |
| 15 | He didn't receive treatment in covid 19 |
| 16 | Occupational therapist and speech and language appointments were 3months+. This was at a critical stage where we were noticing some significant deterioration in our child abilities. |
| 17 | Non are applicable as [redacted] was diagnosed post covid |
| 18 | Appointments with neurologists and paediatricians |
| 19 | speech and language therapy, physiotherapy, occupational therapy, schooling |
| 20 | Schooling |
| 21 | mental health services, |

116) Please use your own words to describe the impact of the COVID-19 pandemic on the child/young person/younger adult in this survey.

| | |
|---|---|
| 1 | The most important was inability to go to school and isolation. It affected mental health and well-being. |
| 2 | During Covid our son was unable to access any therapies or education. This had a massive impact as he relies on weekly physiotherapy and hydrotherapy for his muscle tightness. We were also unable to get hold of any equipment, as professionals were |

| | |
|---|---|
| | unable to come out and do any assessments. The social aspect of Covid also played a huge impact on his wellbeing as he became confused as to where everyone had gone. Our son is one of five siblings therefore we normally have a very busy and loud house which suddenly during Covid turned very quiet. The impact of Covid was negative due to the lack of therapies however it also had a positive impact as we were all able to spend time together as a family something which is our busy household is rare. |
| 3 | Most significant was that it prevented access to regular day centre, college and exercise such as swimming |
| 4 | During this period, because of the lack of access to therapies, including physio, horse riding, SALT his condition deteriorated. |
| 5 | COVID solves down my daughter diagnoses of Batten Disease. |
| 6 | We were post COVID so non applicable to us |
| 7 | During the lockdown our daughter started to lose her vision. She/us had no support from any specialists. We could not get her seen by anyone or get support/advice from professionals. |
| 8 | Awful. The mainstream school happily abandoned [redacted]. We had no access to vital services such as physio. I had to isolate with my 2 children for more months to shield [redacted]. She lost out on valuable social interactions, therapies etc |
| 9 | We were diagnosed during the pandemic and so we had very few services available to us at diagnosis. |
| 10 | Still got treatment and she is still alive - so the pandemic did not impact on treatment She stayed well |
| 11 | In some ways, it was positive for us to have every day at home with our child as we were able to notice the changes. Her symptoms, beyond speech delay, only began during lockdown. Negatively though, there was an impact in how services stopped i.e MRI |
| 12 | [redacted] lost a lot of strength in the pandemic he had only been diagnosed for a little over a month and when lockdown came, we had no equipment or training available to us, even after the pandemic was over it took so long to receive equipment because of the backlog to the point we were lending equipment from his school. |
| 13 | Genetic testing took longer. All services were done over zoom. Paediatrician refused to see daughter face to face. They also blamed developmental delays on the pandemic even though she accessed nursery the entire time. |
| 14 | The delay in appointment overall slowed our child diagnosis down. |
| 15 | Health wise, there was no impact. Socially - it prevented our child from developing & interacting with her friends. Educationally - our daughter missed out on the structure and regularity of lessons, which included speech and language assistance. |
| 16 | The epilepsy panel was delayed due to covid. Appointments to see the local neurologist as well as a specialist neurologist were delayed. Diagnosis in my opinion was extremely delayed. |
| 17 | We were isolated from my extended family |
| 18 | As with anything during the pandemic, everything was extra stressful, but thankfully Covid did not impact treatment! |

**PART 7**

**Carer Views on Assessments Used During the MAA Process**

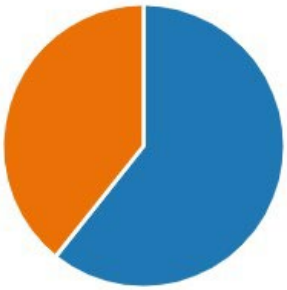
117) Do you think that your experiences (clinical, physical, emotional and psychological), and those of the child/young person/younger adult in this survey, were captured adequately by the MAA tests and assessments? If no, please provide further details below.

| | |
|---|---|
| Yes | 16 |
| No | 12 |



118) Thinking about physical outcomes, do you think that your experiences, and those of the child/young person/younger adult in this survey, were captured adequately by the MAA tests and assessments? If no, please provide further details below.

| | |
|---|---|
| Yes | 17 |
| No | 11 |



119) Thinking about emotional and psychological outcomes, do you think that your experiences, and those of the child/young person/younger adult in this survey, were captured adequately by the MAA tests and assessments? If no, please provide further details below.

| | |
|---|---|
| Yes | 14 |
| No | 13 |



120) If your answers to Q117-Q119 were "No", please provide further details.

| | |
|---|---|
| 1 | Psychology test inadequate. Questions for example if my daughter has suicidal thoughts or thinks about using weapons are inappropriate. Test proves what she cannot do but doesn't show what she can do and how she improves. All test focus on what they cannot do instead of showing how they improve and doing great despite disease. EEG ECG and MRI is very stressful and very upsetting. We never got results back so not sure what they're trying to achieve by theses test either. It all feels like box rocking exercise. It feels professionals don't care about wellbeing of our children. Daily hospitals visits every 2 weeks should be enough and children shouldn't be put through any more stress. |
| 2 | All the MAA assessments took place either before or after the enzyme replacement therapy. Apart from the assessments which took place in the last 12 months all were done in Great Ormond Street Hospital, London. Our son was tired when these assessments took place. He had travelled for a number of hours, sometimes he had a few hours sleep in the patient hotel in an uncomfortable bed, sometimes he had already been awake since 2am. He would then have observations taken, then a four-hour brain infusions and then he would have MAA assessments. He would be overtired and would not want to participate in anymore assessments. Some of these assessments would not take into account vision loss and children would be marked down unable to perform a certain task when that task was completely impossible for a child with no vision to complete. It is unacceptable to ask a tired child who already experiences difficult with movement to performed when asked in-front of strangers and sometimes cameras when they are feeling vulnerable and tired. Some of the assessments for example vision assessments can be very uncomfortable again true reading will be unable to be obtained from children who are upset and unsettled. |
| 3 | Physio reviews are a snapshot and don't really take into account day to day life. Psychology tests don't feel particularly relevant due to communication difficulties. |
| 4 | The psychological tests were often done using pictures that were not very clear and often ones that did not interest our child. So, he was quite bored and therefore got marked as not knowing what a fork is (for example) even though he does know what a fork is. |
| 5 | Assessments non uniform across centres/different professionals. Tests subjective. Too open to interpretation, little guidance for parents. Do not capture the essence of the child. Feels like tick box exercise for NICE. Eye tests uncomfortable and distressing for children. ERT does not protect vision so unnecessary for MAA |
| 6 | Often Children with metabolic disorders feel uncomfortable in new or different environments, and ALL the MAA tests are conducted by individuals who don't have any relationship with the child; in environments where the child is not calm/familiar with. Likewise, some of the equipment is inadequate for the tests - i.e. OCT rental scanners. It requires the child to put their chin on a strap and follow instructions to get results. [redacted] simply refused, and Bristol didn't have a handheld one. |
| 7 | I think the focus should be how they interact at home and school. Along with what they enjoy and life experiences/quality of life. The survey does not bring the child to life. Assess across settings to ensure you capture the real child and their personality - not just a snapshot. factors like different lifestyles are not considered - depends on family dynamics and circumstance. |

| | |
|---|---|
| 8 | The tiny snapshot of time that the assessors see our child and at a time when they are usually tired and in an unrelaxed/unfamiliar environment, never captures our child at their best. It also seems an almost impossible task to capture a person in all their spectrum of abilities with black and white data. Most recently our ophthalmology assessments were done at a centre without specialist equipment which made it near impossible to get any sort of data. |
| 9 | The children aren't preforming monkeys. They don't want to engage with people their unsure of and if it's a new setting they would rather explore and have a nosey then sit and do what they are asked unfortunately. Also, kids with Battens don't always do things as black and white as it's asked. For example, the way they get asked questions in the phycology assessment, sometimes they won't understand the way it's said, and it's not allowed to be asked any other way (names of things, the wording used isn't familiar to understand) |
| 10 | The psychology tests were not reflective and not appropriate for our children. My child can do 90% of the things in the test but she would not do it in a hospital setting. Local therapists should be able to conduct these assessments at home where the child is comfortable and going about daily life. |
| 11 | Q116-Q119 - we answered 'no' because we feel the MAA questions do not allow for parents to provide real world/real life data and examples. Whilst we understand the necessity to have quantifiable data, our children are doing amazing things that are not captured because the assessments are only capturing that child on one specific day to show what they can do. They may be feeling tired, unwell, just not in the right mood so their responses may not be an accurate reflection of their abilities and skills. We feel sense of humour, character traits and abilities that the child would show at home or at school are a far more accurate and fair reflection of their everyday life. When you are deciding on the viability of a drug that means the difference between life and death, there should be an allowance for the addition of real-world evidence from home, clubs, leisure activities, social situations through videos and photos and even visiting the child in person. That is what would be the ideal as if the child has an 'off day' on assessment day, there is nothing we can do. In our particular case, our daughter has been acquiring skills and abilities which have never been seen before in a child with CLN2 at this age (8) and as such we feel this amazing and unique situation was not significantly capturing how remarkable our child is and how remarkable the treatment has been for our child. |

121) How well do you think the tests and assessments used during the MAA worked in measuring the effectiveness of the treatment?



122) What outcomes do you think have not been assessed or captured in the MAA data?

| | |
|---|---|
| 1 | I've never received the data so can't comment. Seems like professionals don't like sharing they're results or discussing with parents |
| 2 | The link between vision loss and mobility loss. Also, the psychology assessments are not fit for purpose for those children with vision loss. For example, a child with full vision may be able to recognise colours and letters. When this child vision deteriorates the assessments will show that this child can no longer recognise the same colours and letters as they could at their last assessment. This child will lose points on the rating scale. However, the reason they can no longer recognise the colours and letters is due to the loss of vision not loss of skills. |
| 3 | Knowledge and extent of retained knowledge. Personal skills. Interaction with trusted close family / friends / true character. |
| 4 | The quality of life, happiness, |
| 5 | Data should have been collected as case studies, not tick boxes. Sample size relatively small so would be achievable |
| 6 | Quality of life. The time it gives back to children in terms of lifespan. |
| 7 | Depends on parents' frame of mind at time of MAA survey. The progression of the disease impacts on parents' emotional wellbeing and this in turn can impact on responses (for example if the child is unwell at the time) |
| 8 | How do you capture and measure quality of life via a process of tick boxes? |
| 9 | The true picture of the children, they don't get a clear view of how amazing the child is. If it's been a bad night or their having a bad day. This reflects on their assessment and willingness to engage. |
| 10 | Nothing, I think it covers everything. |
| 11 | I think it's important for them to be assessed in terms of what they can do instead of what they can't. Her school and local services have not been able to provide their insight of her abilities and therefore it is all gone of what she can show in hospital which is nothing in comparison to what she can actually do. |
| 12 | The true cognitive abilities of my child. The words he can say, the knowledge he has despite being 7 with Batten Disease. The day to day he experiences, the love and zest he has for life, for his school, his friends, his family, he loves rollercoasters, fast rides and meeting his favourite characters at theme parks. The assessments do not capture his true quality of life, which is full of fun, laughter and love. |

123) In your opinion, were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective? Please give details below. In your answer, please consider the following points: (a) duration of assessment, (b) type of assessment, (c) frequency of assessment, (d) difficulty of assessment, (e) unnecessary repetition of assessment.




124) In your opinion, were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective? Please give details below. In your answer, please consider the following points: (a) duration of assessment, (b) type of assessment, (c) frequency of assessment, (d) difficulty of assessment, (e) unnecessary repetition of assessment.

| | |
|---|---|
| 1 | EEG ECG psychology testing |
| 2 | Psychology assessments were difficult due to the duration of the assessment. The assessments were long and in unsuitable environments. There were often lots of distractions. For example, expecting a child to sit at a table with a picture book whilst the rest of the room was full of toys. The correct concentration from the child would not be available. Assessments on the eyes were extremely hard. Long wait times in the waiting room for the assessments. Along with eye drops which sting and upset the child before again wanting them to perform to strangers after a long infusion day. Also, the eye assessments where unnecessary to continue once a child had full vision loss |
| 3 | No difficulties of note |
| 4 | The EEG was a horrible assessment with flashing lights and done every 6 months and it had no clinical reason. |
| 5 | They are all difficult due to [redacted] nature of the disease and age. But we know they are needed. |
| 6 | All of it. Please see previous |
| 7 | We had several EEG's which had the same outcome and seemed pointless, the first blood tests both parents had said there was no genetic disease but then came back as there was |
| 8 | Retinal scans....Very harsh, emotionally tough, and there isn't a treatment available to help slow the regression. They are also long, and seizure triggering and come around very quickly. EVERY carer/parent hates them. |
| 9 | There were multiple instances where tests were repeated over and over again which was stressful for everyone due to the constant hospital visits. |
| 10 | Yes, this is an example of repetitive questions |
| 11 | Difficulty of assessment - when moving from GOSH there has been teething problems with a new service beginning. This has been felt with professionals having an unfamiliarity with our child. Psychological assessments were attempted four times and initially with age related activities/questions. Equipment in ophthalmology that was substandard to that of GOSH and so struggled to get our child through a torturous test only to be unsure any data was captured. |

| | |
|---|---|
| 12 | Ophthalmology assessments - pointless when a child is blind |
| 13 | I found the phycology assessment was the worst, they asked absolutely stupid questions, and it was just read of a sheet. Can they read “no” can they read a book” …. Unnecessary and not catered for. Would be helpful to get a Questionnaire together tailored for CLN2 children with a better understanding of their needs, ability’s etc and maybe get it to be completed at schools or by professionals who see them on a daily basis and can fill that in on an overall basis and they’re not judged if it’s a bad day or good day on top. |
| 14 | We travelled to London every fortnight for two years for [redacted] treatment (3 hours 15 minutes one way) which meant overnight stays and being away from our daughter. Sometimes only for a 30-minute appointment. |
| 15 | The MRI is difficult because it means putting the child under GA. Children with batten disease are affected by GA’s so this is counterproductive and unnecessary additional trauma for the child. The psychological assessment is not effective and should be done by local professionals in the home/school setting. Eye tests are also pointless since we all already know that Brineura does not help with vision. |
| 16 | No |
| 17 | We feel that the location and environment of where the assessments were held was not set up for a positive experience. The one in particular I am referencing is the psychology assessments in the basement in GOSH. The room was very clinical, the table and chairs were not always suitable, and our daughter spent a good few minutes trying to get comfortable in her seat to reach the table. It was not a welcoming, encouraging, warm setting which would have been a stimulating room to encourage the child to feel happy and settled and comfortable. Not having the best room/seating/table/setting was not the most comforting setting - if our daughter is not comfortable, she will not perform as well as she could. I felt frustrated because the room was not centred about the child, and it was not welcoming or friendly. The people carrying out the assessment were wonderful though I must add! Another thing that I would incredibly frustrating was the fact that we were not allowed to interject in anyway. I was at one assessment, biting my hand to stop myself from speaking & it took so much self-restraint to not interrupt. The words that were prescribed in the questions, were not always words we would use at home, so our daughter was not familiar with that reference. I was wanting to say "if you just said it in a different way, she would understand and could then answer your question!".....but I had to watch as my child struggled and didn't get the answer correct. I would always say "I know she knows that, but we don't use that word or phrase at home". It was incredibly frustrating. |
| 18 | I didn’t experience any of the above difficulties. |

125) Please use the space below to tell us anything else you would like us to know about your experiences of the MAA process.

| | |
|---|---|
| 1 | Life changing treatments are widely available on NHS and people don’t have to fight for the treatment to be available. But we do. And our children have to go through unnecessary tests that prove nothing just cause upset and stress. Isn’t it enough to be told that your child has terminal disease and there is treatment that can slow it down? Why do we have to fight for it. Isn’t it human right of our children that if treatment is proven to be working it’s unethical to even think of taking it away? |

| | |
|---|---|
| 2 | It would have been nice to know as parents our children's results, so we knew which areas to work on. For example, if our child was struggling with something in regard to physiotherapy this could have been worked on within the community. |
| 3 | The psychological assessments were not very good and did not get a good reflection of my child's understanding or abilities. |
| 4 | As mentioned, it's difficult to attend all assessments and get the readings we need but that is due to the nature of the disease along with [redacted] age, so we struggle to get good results as is. |
| 5 | Apart from believing that some of the MAA assessments are not fit for purpose, our children have coped very well with all the assessments. |
| 6 | I hate it |
| 7 | I would prefer to have a conversation about this as I have many views that I need to share |
| 8 | It would've been great to have an objective view (possibly an OFSTED type body) to assess whether this MAA was achieving what it was set up to capture. |
| 9 | It's been very traumatic waiting for this review, not knowing if a treatment that is keeping your child alive is going to be taken away. It's hard to understand how the benefits of Brineura are not obvious to NICE (especially in children diagnosed prior to 4yo) and our children deserve to live. Feeling like there is a price tag on your child's life is utterly heartbreaking. |
| 10 | When completing the MAA for our older daughter who is no longer with us, i found the questions in the telephone calls extremely upsetting. She was fully dependant on us for everything, yet I had to sit and answer a series of questions which were not applicable such as "can your child wash herself?" "Can you child dress herself?". It was very upsetting to have to listen to each question and almost be reminded just how much she could no longer do. There should have been a way of making that section not applicable to prevent parents from having to answer "no" to everyone. |
| 11 | I do not have a problem with the extra testing that has been needed but to assess my son's quality of life with Quality-of-Life questionnaire seems absurd. Some of the questions were completely irrelevant and do not show how amazing his life is and the fun and joy he experiences each day. Yes, his life could be better – but only if he didn't have Batten Disease. We do everything we can to ensure he is healthy and happy. |

**PART 8**

**Daily Life**

126) For the child/young person/younger adult in this survey, how has their schooling been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 6 |
| Slightly affected | 22 |
| Unable to join in | 3 |



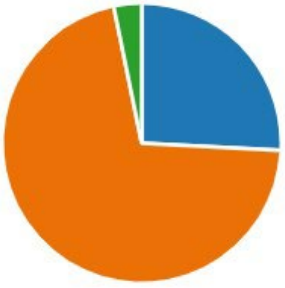
127)For the child/young person/younger adult in this survey, how has their ability to play with friends been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 11 |
| Slightly affected | 14 |
| Unable to join in | 6 |



128) For the child/young person/younger adult in this survey, how have their family activities been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 8 |
| Slightly affected | 22 |
| Unable to join in | 1 |



129) For the child/young person/younger adult in this survey, how has their ability to watch TV been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 21 |
| Slightly affected | 8 |
| Unable to join in | 2 |



130) For the child/young person/younger adult in this survey, how has their ability to play games been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 5 |
| Slightly affected | 14 |
| Unable to join in | 12 |



131) For the child/young person/younger adult in this survey, how has their imaginary play been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 10 |
| Slightly affected | 11 |
| Unable to join in | 10 |



132) For the child/young person/younger adult in this survey, how have their hobbies been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 8 |
| Slightly affected | 16 |
| Unable to join in | 7 |



133) For the child/young person/younger adult in this survey, how has their self-care (dressing, cleaning teeth etc.) been affected by having CLN2 Batten disease?

| | |
|---|---|
| Not affected | 3 |
| Slightly affected | 13 |
| Unable to join in | 15 |



134) For the child/young person/younger adult in this survey, have other activities have been affected by having CLN2 Batten disease (please specify)?

| | |
|---|---|
| Not affected | 6 |
| Slightly affected | 11 |
| Unable to join in | 3 |
| Other | 7 |

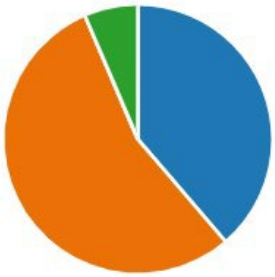


Other:

| | |
|---|---|
| 1 | Whole life activities have to be adapted to child's needs |
| 2 | Condition prevents from taking part in many activities and age-related activities |
| 3 | hygiene |
| 4 | Family holidays are limited to wherever is most accessible |
| 5 | Every aspect of our lives have been affected |

135) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their schooling?

| | |
|---|---|
| Not affected | 12 |
| Slightly affected | 17 |
| Unable to join in | 2 |



136) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their ability to learn new skills?

| | |
|---|---|
| Not affected | 16 |
| Slightly affected | 9 |
| Unable to join in | 6 |



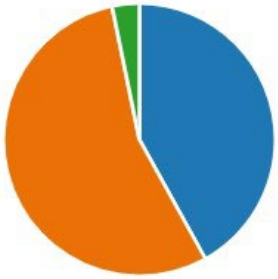
137) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their ability to play with friends?

| | |
|---|---|
| Not affected | 18 |
| Slightly affected | 9 |
| Unable to join in | 4 |



138) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their family activities?

| | |
|---|---|
| Not affected | 13 |
| Slightly affected | 17 |
| Unable to join in | 1 |



139) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their ability to watch TV?

| | |
|---|---|
| Not affected | 23 |
| Slightly affected | 6 |
| Unable to join in | 2 |



140) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their ability to play games?

| | |
|---|---|
| Not affected | 12 |
| Slightly affected | 13 |
| Unable to join in | 6 |



141) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their imaginary play?

| | |
|---|---|
| Not affected | 16 |
| Slightly affected | 9 |
| Unable to join in | 6 |



142) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their hobbies?

| | |
|---|---|
| Not affected | 14 |
| Slightly affected | 10 |
| Unable to join in | 7 |



143) For the child/young person/younger adult in this survey, how does the treatment with Brineura affect their self-care?

| | |
|---|---|
| Not affected | 10 |
| Slightly affected | 8 |
| Unable to join in | 12 |



144) For the child/young person/younger adult in this survey, does the treatment with Brineura affect any other activity (please specify below)?

| | |
|---|---|
| Not affected | 12 |
| Slightly affected | 7 |
| Unable to join in | 4 |
| Other | 4 |



Other: We have to plan family trips and holidays around the treatment

145) Please use your own words to tell us more about your responses to Q135-Q144

| | |
|---|---|
| 1 | Although our son's abilities have been affected massively since he was diagnosed most of his skills were lost before he started treatment. Since starting enzyme replacement therapy our son has remain stable. We are very lucky to have a large and inclusive family. As parents we also belief that at disability does not define you as a person. Where we go as a family our son goes too. We do not have carriers out of personal choice. Our son has many friends, family members and siblings who take care of him and include him in daily activities. Although some activities maybe more difficult to access due to his condition we will adapt these activities to meet his needs. We find that it is the world that we live in that makes life harder for us to access as many places as we would like due to places being inaccessible for the disabled. |
| 2 | Our daughter is impacted by her loss of vision, we are lucky to mainly have a system in place to adapt to her needs but this does not happen everywhere or in every situation. |
| 3 | [redacted] is able to engage in activities more so in the days following ERT |
| 4 | [redacted] is now in a special school and has 1-1 care. All other children in the school are neuro-diverse so [redacted] engages as much as they are also able to. Family activities - we always try and do activities where [redacted] can join in, however it does restrict the type of activities available. |
| 5 | I am struggling to understand how accurate data can be gathered from the answers to these questions. I feel very disappointed with this survey. It is not giving us parents the opportunity to explore and report the benefits of the treatment. There are not enough answer options to share details of our children and some questions are not applicable. |
| 6 | While there is difference in our family to those families with unaffected children, our family has adapted and continues to adapt in how we play together and interact. There is so much laughter and happiness in our home. |

| | |
|---|---|
| 7 | CLN2 disease massively impacts every aspect of my child's life |
| 8 | [redacted] has a movement disorder which effects the movement in his hands so is unable to do a lot when it comes to joining in games and playing, he is also in a wheelchair so needs 24-hour care which impacts certain things he can join in with. |
| 9 | I don't think haven the treatment affects him doing anything, it's brought him better on |
| 10 | Brineura is allowing our daughter to be able to attend school, to play with friends, to go to ballet class, to ride her scooter. It is having a hugely positive impact. |
| 11 | Brineura has helped our son to keep his cognitive abilities, he is still attending school full time and loves playing with his friends. He is not as able to play the games he used to play such as board games and football in the same way but with the help of others, aids, therapy he can access so much still. |
| 12 | My child has always been dependent on me to provide healthcare with encouragement and to learn. My child is 13 but has delayed development that I assume he would have without batten disease. |

146) Has receiving Brineura changed your ability to go on holiday as a family?




147) Please use your own words to tell us more about your responses to Q146.

| | |
|---|---|
| 1 | We are very thankful to be able to still go aboard as a family, however it is not easier. It is hard to fly due to planes being inaccessible for the disabled. However, we make it work. |
| 2 | We are still able to fly with our daughter however it does take more organising. We are lucky to be able to travel quite often. Our daughter goes aboard 4 times a year. |
| 3 | [redacted] appears to be more switched on following infusion, more energy etc too |
| 4 | We just have to think about what dates are available more with regards to holidays and when treatment days are. Treatment can accommodate a +-3 day flexibility on the odd occasion though which we appreciate. |
| 5 | Treatment does not prevent holidays. If it was not for Brineura she would have died at the age of 5. So, this treatment has given us the opportunity to have several family holidays creating memories! |

| | |
|---|---|
| 6 | We only go on holidays locally, too much travel is too stressful and leads to seizures. We would not manage going on holiday abroad. |
| 7 | We have to prepare more, think about access and make sure they are catered for, hospitals nearby, insurance etc but it isn't an issue just have to be more prepared |
| 8 | We are able to go on holiday, but we mainly stay in the UK because of health reasons. |
| 9 | We have always gone on holiday and our daughters health is so good because she is on treatment that she is like any other child of her age so the reason we put 'no change' is because our daughter is able to continue to come on family holidays as she always has..... |
| 10 | We plan our holidays around infusions |

**PART 9**

**Carer Information**

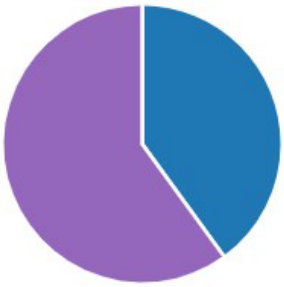
148) How often do you care for the child/young person/younger adult in this survey?

| | |
|---|---|
| Full time | 26 |
| Part time | 5 |



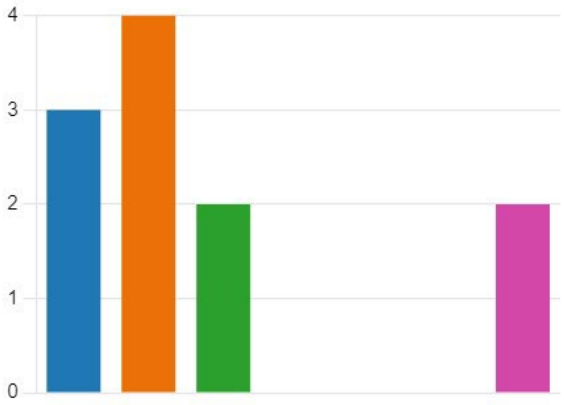
149) If you care for the child/young person/younger adult in this survey in a part-time capacity, when are you involved?

| | |
|---|---|
| Several hours per week across d... | 2 |
| Several hours per day, mornings... | 0 |
| Several hours per day, afternoo... | 0 |
| Several hours per day, evenings ... | 0 |
| Weekends only | 3 |



150) If you care for the child/young person/younger adult in this survey in a part-time capacity, who looks after them when you are not there (please select all that apply)?

| | |
|---|---|
| Mother | 3 |
| Father | 4 |
| Grandmother | 2 |
| Grandfather | 0 |
| Sibling (18+) | 0 |
| Guardian | 0 |
| Other (please specify) | 2 |



151) If you are a full-time carer, do you have access to respite help?

| | |
|---|---|
| Yes | 16 |
| No | 13 |



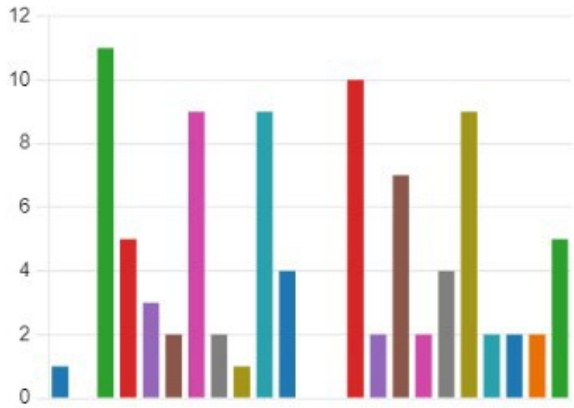
152) In response to your answers to Q151, if you would like to, please use your own words to tell us more about the type of respite help you receive and from whom below.

| | |
|---|---|
| 1 | We're not aware there is any respite help available |
| 2 | Myself and my husband are the main carers for our son. We have a great family network of support. We chose not to use respite services. |
| 3 | Family, local hospice. |
| 4 | It is personal choice not to use respite |
| 5 | [redacted] stays at her dads sometimes on a Saturday eve |
| 6 | We care for the child at the weekend but often have her extra will sometimes have her for a week or extra days and extra for treatment, her mother is supposed to look after her in the week but mainly the grandmother cares for her as her mother works and goes on holiday, so she is then shared between us and the grandmother. We have weekends off when going on holiday and will then have the child extra to make up for the day's lost. |
| 7 | Hospice carers who come out once a fortnight for 3hrs. Direct payment carers 7hrs per week to allow us to do shopping/cleaning/extracurricular activities with siblings. |
| 8 | My daughter stays with myself and my partner and also with her grandmother/mother. Her Grandparents are usually the main carers for her due to her Mum working. |
| 9 | Was a long fight to get any respite and support |
| 10 | Hospice carers and DP workers come to our home. |
| 11 | Local children's hospice |
| 12 | We have a PA for restbite. |
| 13 | She goes to a children's hospice for one Saturday or Sunday per month (Zoe's place). She loves it there. |
| 14 | We have applied for help with respite care and are waiting for it to be organized. Like everything else it seems to take a long time. |
| 15 | Both myself and my wife look after him at certain times of the week, we also have a care package from the local authority and NHS so we have carers coming in morning and evening on weekdays |

| | |
|---|---|
| 16 | We have employed PA's who come and look after our daughter or take her out on their own or they accompany us on our family trips out. This is our main source of respite as well as receiving 2 hours once a month from Rainbow Trust. |
| 17 | Rainbows children's hospice, 3 stays per year as a family |
| 18 | My son has 13 to 14 days a year respite |
| 19 | We both work full time and have a full-time carer for child |

153) From the list below, please choose the THREE symptoms which you find the most challenging to manage with the child/young person/younger adult in this survey as their carer.

| | |
|---|---|
| Chronic seizures | 1 |
| Disease related stress | 0 |
| Clumsiness and issues with coor... | 11 |
| Dystonia | 5 |
| Myoclonus | 3 |
| Limb weakness | 2 |
| Vision loss | 9 |
| Feeding or swallowing difficulties | 2 |
| Respiratory difficulties | 1 |
| Problems with speaking | 9 |
| Changes in mood and/or behavi... | 4 |
| Hallucinations | 0 |
| Pain | 0 |
| Sleep disturbances | 10 |
| Fatigue/tiredness | 2 |
| Lifting | 7 |
| Washing | 2 |
| Child/children/young person(s)/... | 4 |
| Giving medication | 9 |
| Schooling | 2 |
| Getting an EHCP in place | 2 |
| Other (please specify) | 2 |
| Other | 5 |



154) How would you rate your general health?

| | |
|---|---|
| Very good | 7 |
| Quite good | 11 |
| Neither good nor poor | 10 |
| Quite poor | 3 |
| Very poor | 0 |



155) Do you think that caring for the child/young person/younger adult in this survey has an impact on your physical health?

| | |
|---|---|
| Yes | 25 |
| No | 6 |



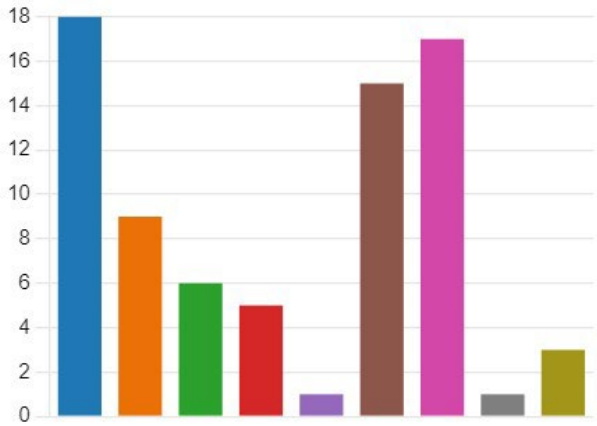
156) Has caring for the child/young person/younger adult in this survey become more manageable since they started to receive Brineura?

| | |
|---|---|
| Yes | 16 |
| No | 11 |



157) Which of the following activities have the greatest impact on your physical health (please select all that apply)?

| | |
|---|---|
| Physical lifting | 18 |
| Physical carrying | 9 |
| Feeding | 6 |
| Child/children/young person(s)/... | 5 |
| First aid/emergency care (e.g., s... | 1 |
| Lack of sleep | 15 |
| Lack of personal time | 17 |
| Other (please specify) | 1 |
| Other | 3 |




158) How would you rate your mental health?

| | |
|---|---|
| Very good | 3 |
| Quite good | 10 |
| Neither good nor poor | 9 |
| Quite poor | 7 |
| Very poor | 1 |



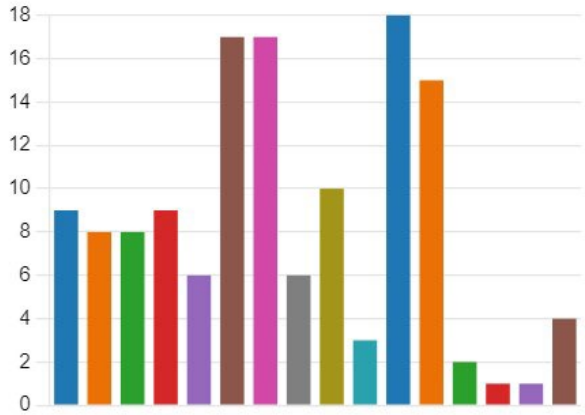
159) Do you think that caring for a child/young person/younger adult with CLN2 Batten disease has an impact on your mental health?

| | |
|---|---|
| Yes | 26 |
| No | 4 |



160) Which of the following have the greatest impact on your mental health (please select all that apply)?

| | |
|---|---|
| Lack of emotional support | 9 |
| Lack of financial support | 8 |
| Lack of physical support | 8 |
| Lack of suitable child/children/y... | 9 |
| Adhering to the treatment timet... | 6 |
| Uncertainty | 17 |
| Anxiety | 17 |
| Guilt | 6 |
| Depression | 10 |
| Child/children/young person(s)/... | 3 |
| Lack of sleep | 18 |
| Lack of personal time | 15 |
| Schooling | 2 |
| Getting an EHCP in place | 1 |
| Other (please specify) | 1 |
| Other | 4 |




161) How would you rate your social wellbeing?

| | |
|---|---|
| Very good | 4 |
| Quite good | 11 |
| Neither good nor poor | 9 |
| Quite poor | 6 |
| Very poor | 0 |



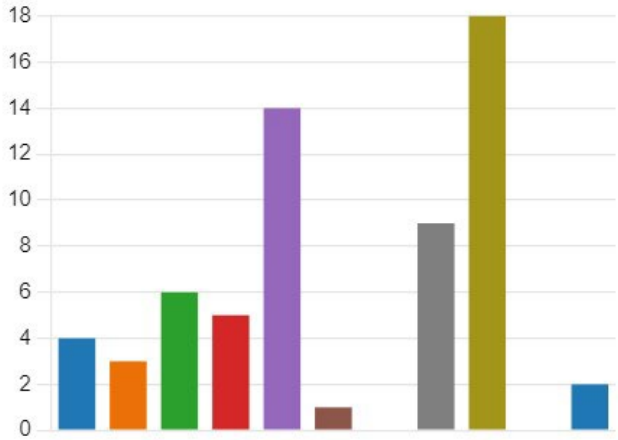
162) Do you think that caring for a child/young person/younger adult with CLN2 Batten disease has an impact on your social wellbeing (i.e., social isolation)?

| | |
|---|---|
| Yes | 25 |
| No | 5 |

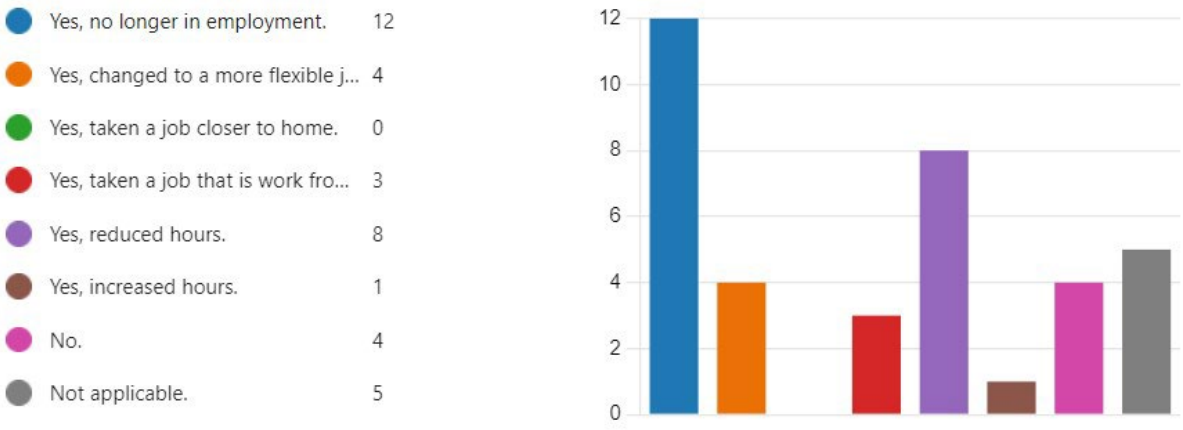


163) Which of the following have the greatest impact on your social wellbeing?

| | |
|---|---|
| Lack of emotional support | 4 |
| Lack of financial support | 3 |
| Lack of physical support | 6 |
| Lack of suitable child/young per... | 5 |
| Uncertainty | 14 |
| Adhering to the treatment timet... | 1 |
| Child/children/young person(s)/... | 0 |
| Lack of sleep | 9 |
| Lack of personal time | 18 |
| Other (please specify) | 0 |
| Other | 2 |



164) Has caring for the child/young person/younger adult in this survey had any impact on your career/ working life (please select all that apply)?




165) Has caring for the child/young person/younger adult in this survey had an impact on your family's finances?



166) Has caring for the child/young person/younger adult in this survey had any impact on your education?

| | |
|---|---|
| Yes | 5 |
| No | 8 |
| Not applicable | 17 |



167) If yes, please describe this impact.

| | |
|---|---|
| 1 | I had to postpone post graduate education due to lack of time and hospital commitments also due to financial difficulties |
| 2 | I did not work before diagnosis however I have been unable to return to work if I had wanted too. |
| 3 | Lack free time means I cannot attend courses |
| 4 | A lot less finances to be able to "do" things both with family and friends. Likewise sleep deprivation means we are knackered at night, and we are unable to pay for night carers. Likewise, council won't pay for night carers until it is end of life care. We have gained experience and knowledge that we wouldn't have had and are able to pass this onto other newly diagnosed families. It's a VERY intense education. Likewise, now being unemployed means we are becoming less "employable" to future companies due ageing working knowledge. |
| 5 | I find the mental load of being a CLN2 parent so all-consuming that it can be tricky to think about much else at times. My husband and I are in a place where we have both stopped work for a time to look at what we are going to change in our roles to make employment more manageable for our family. We are looking to both work part time in self-employment. |
| 6 | I only work part time now, |
| 7 | I still work but my wife had to leave her job to provide full time care to our child. This was before he was placed in a specialist school. |
| 8 | As a Neurosurgeon by profession, I had to give up my aspirations of returning back to India and compromise significantly with my career prospects, having to give up a lot of my skills and area of work to stay in UK and carry on working alongside supporting my child and family. My wife had to give up her career completely as a dentist. |

168) Does caring for the child/young person/younger adult in this survey affect your ability to travel?

| | |
|---|---|
| Yes, a lot. | 5 |
| Yes, somewhat. | 14 |
| Yes, rarely. | 2 |
| No | 9 |



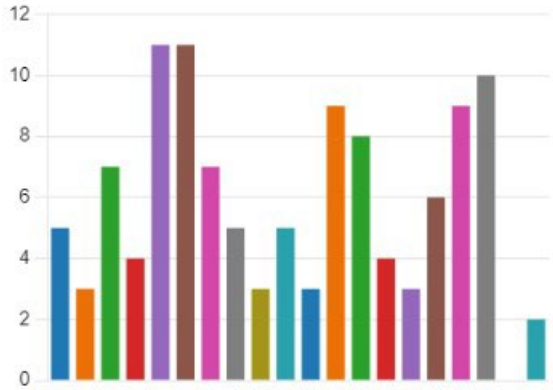
169) Please use the space below to tell us about anything else that caring for the child/young person/younger adult in this survey impacts your life.

| | |
|---|---|
| 1 | Holiday cost is higher due to disability. Expenses with hospital visits. Unable to do things normal children's families could do due to disability |
| 2 | Makes it tough going out anywhere as we need more items. Makes making plans tough as caring for her isn't as easy especially with medication etc., lack of sleep is tough on relationship and lack of personal time also. |
| 3 | It is harder to have time to myself or time together with my husband, other children. |
| 4 | hard to describe |
| 5 | I sometimes struggle as I don't have a partner. [redacted] father left us shortly after diagnosis. |
| 6 | Travelling - we are unable to fly due to lack of airplane disabled seats, and anywhere with a timezone difference is likely to disorientate [redacted] sleep further - meaning for an expensive stressful experience in an unfamiliar environment without equipment. Travelling in the UK is fine due to private vehicle - despite expensive fuel for a van. |
| 7 | Having a terminal child would impact on any parents life |
| 8 | Being a parent to a CLN2 child is a constant journey of learning how to live again. There isn't one place in life it hasn't altered. |
| 9 | The anxiety and uncertainty regarding the ongoing negotiations for long term access to Brineura has been excruciating and very painful and are never far from our thoughts as we try to live our lives and care for our children and give them the love and attention they need. Not only are we faced with the challenges of life with a child with a rare disorder (where you have to fight for everything and nothing is easy) we have had to endure years of uncertainty as to whether our daughter will be given the chance to continue to receive this transformative medicine which is clearly been proven to work. All around the world, we see children receiving this and whilst we appreciate every country has its own health care systems and policies, we have had to live with another cloud over our heads as we have waited and campaigned for children in the UK to have access to the one and only treatment that is available for their condition. It has had a huge impact on our lives because how can we be expected to live our lives knowing that decisions and negotiations |

| | |
|---|---|
| | are being held about the life of our child? It is impossible but we have kept going, kept focussed and we will continue to do this until we get the YES that our children deserve. The first negative decision was incredibly and deeply stressful. The pressure to speak up, to be involved in campaigning, to be active in the fight for this treatment was all consuming. It was absolutely exhausting, mentally, physically and emotionally and we feel that families deserve a YES. We deserve to know that our children will not be taken off treatment. We deserve to know that children who are going to be diagnosed in the weeks, months and years to come, do not have to wonder and suffer. Children should be given access to Brineura. It is a proven treatment; they have a right to life and Brineura is the single option to give them that. Every child deserves a chance. |
| 10 | Travel needs to be coordinated around his bi-weekly infusions |

170) Since starting on Brineura, has there been any change in the impact of your caring responsibilities for the child/young person/younger adult in this survey (please select all that apply)?

| | |
|---|---|
| Lack of emotional support | 5 |
| Lack of financial support | 3 |
| Lack of physical support | 7 |
| Lack of suitable child/children/y... | 4 |
| Uncertainty | 11 |
| Anxiety | 11 |
| Guilt | 7 |
| Depression | 5 |
| Adhering to the treatment timet... | 3 |
| Schooling | 5 |
| Getting an EHCP in place | 3 |
| Physical lifting | 9 |
| Physical carrying | 8 |
| Feeding | 4 |
| Child/children/young person(s)/... | 3 |
| First aid/emergency care (e.g., s... | 6 |
| Lack of sleep | 9 |
| Lack of personal time | 10 |
| Other (please specify) | 0 |
| Other | 2 |



171) How do you feel about the future?

| | |
|---|---|
| Very positive | 1 |
| Somewhat positive | 5 |
| Neutral | 12 |
| Somewhat negative | 6 |
| Very negative | 4 |



172) Please use the space below to tell us about your hopes and concerns about the child/young person/younger adult in this survey and their CLN2 Batten disease.

| | |
|---|---|
| 1 | The hope and concern is in regards to treatment being continued in the future. Concern about vision loss and if she will be able to receive eye treatment. Hope we can but time before any other treatment are available |
| 2 | Although we know what is to going to happen to our children, we choose to live in the now. It would be easy to get caught up in negativity. That's not to say that we don't feel sad and heartbroken but right now our children need us to remain strong. Spending time with them, making memories and giving them the best life possible is all we can do. Enzyme replacement therapy has given us the gift of time, we have been able to create a beautiful life for all of our children something that would have not been possible without this treatment. |
| 3 | Of utmost importance is that treatment with Brineura continues to ensure stability of the condition and continued enjoyment of abilities and life experiences |
| 4 | We are still waiting for the enzyme replacement therapy to be up to properly Start to work as she's not bee. On it for more than 6 months, we are hopeful that this will halt the disease and enable her to have a better quality of life. |
| 5 | Hopes that [redacted] will continue to be at a level where she can still enjoy simple life pleasures and interactions. Concerns about when she does go downhill about care, abilities, physical and emotional impact |
| 6 | I live in terror that the treatment will not be made available and my daughter will die without it. |
| 7 | It is difficult not knowing what is going to happen next, you are just waiting for the inevitable to happen and it has a massive impact on emotional well-being and the difficulties in not being able to do the same things as before even the smallest things of not being able to put the child in the trolley to go shopping because they are unable to sit on their own, I feel that you grieve the child that they were before |
| 8 | We are all trying to enjoy time together whilst being acutely aware [redacted] will pass away much younger than a neaurotypical individual. Likewise, we are also concerned for [redacted] sibling and the effects that the disease is having on him. |

| | |
|---|---|
| 9 | I hope one day there will be a miracle or a cure regarding this nightmare we are living through daily. I am concerned about the uncertainty of the disease as well as the Managed access agreement. |
| 10 | I hope that she remains well and carries on enjoying a happy life. I hope that she is supported to do this by the continuation of her treatment and that people listen to her - she will tell us when she is ready to go My concern is that this is out of our control. Decisions will be made linked to finance agreement between Nice England and pharmaceutical companies |
| 11 | The fear of losing a medication that is making such a difference to our lives by having such an obvious positive effect on our child's life is heavy. Hope is hard to have in our lives because there is constant risk to it getting dashed. And is has many times already. To lose this treatment would be an immediate death sentence to our children and those yet to be diagnosed. This treatment gives us time with the most precious thing our hands and hearts could ever hold. |
| 12 | I am concerned about the slow continued disease progression that we are living with |
| 13 | I feel it's neutral because of the uncertainty of treatments that are going to be available to children with CLN2. |
| 14 | I hope that Brineura is approved for long term use. I believe that Brineura will keep my child stable until a less invasive/continuous treatment comes available such as a gene therapy. |
| 15 | I hope they will be a cure, and my concerns are about the treatment stopping. I'm hoping that they carry on with the treatment |
| 16 | Given this is a terminal and life limiting disease - any decision to stop or delay this treatment is effectively a death sentence. It is currently our only hope. |
| 17 | We have answered 'somewhat positive' regarding the future because we will never lose hope that our daughter will continue to live a healthier and adventure filled life....because of Brineura. However, the ongoing negotiations are very detrimental to parents mental health so the obvious concern is are the NICE committee going to say no again. We will gather ourselves together and never stop fighting.....but that is the point....we should not be using out precious reserves fighting our own country's health care system which has a duty of care for our daughters health. There is only one treatment which is Brineura. There is no alternative. Therefore, we implore the committee and the company to come to an agreement to prevent families for suffering any more than they have done since the EMA approved Brineura back in 2019. Time on this earth is a gift and we want to enjoy the time with our children where we are certain our daughter will continue to have access to the medicine that is keeping her alive and healthy. We want to enjoy many years to come of watching her in her ballet recital, watching her swimming in the sea on holiday, shooting down the slides at the waterpark alongside every other child on holiday. We want to see her build relationships and enjoy her friends and family. This can only be possible if she continues on Brineura. The concern is if treatment stops, we will watch our daughter go from being a miracle child who paved the way for early access to treatment and continues to pave the way with every day she lives and adds new skills to her repertoire, to losing all of her skills.....I can't even bring myself to write what would happen. That is the biggest concern and we will never let that happen. We will never stop until treatment is approved in the UK. |

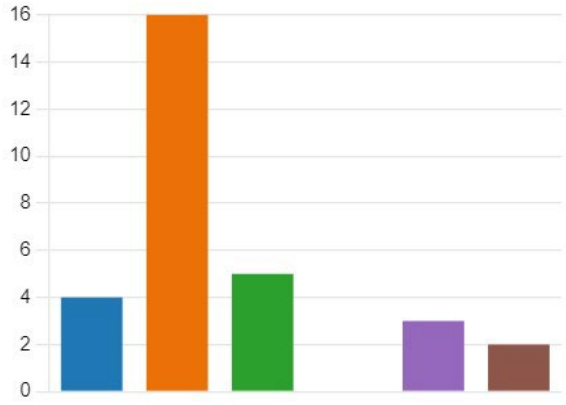
| | |
|---|---|
| 18 | I hope with all my heart that not only does Brineura continue as a treatment but a cure is found. My son deserves life. He is well and thriving and deserves to stay that way just like every other good person on this planet, no amount of money is too much to pay to keep a child healthy and happy. I hope he continues on for many years loving life and school, even as he loses his sight. My only concern is the obvious one and that is seeing him decline and pass away, with Brineura we will get some good quality years of life with him. |
| 19 | I'd hope and dream of the Brineura treatment to be given for as long as it is possible |
| 20 | Child needs his treatment to survive - it is obviously worrying that his treatment could go away. It is hard to make long term plans as we do not have any clarity on childs lifespan - since this is a new treatment. |

**PART 10**

**Siblings**

173) How many siblings does the child/young person/younger adult in this survey have?

| | |
|---|---|
| 0 | 4 |
| 1 | 16 |
| 2 | 5 |
| 3 | 0 |
| 4 | 3 |
| 5 | 2 |



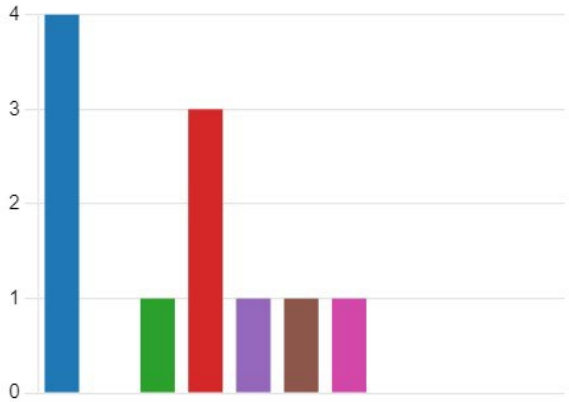

174) How many siblings does the child/young person/younger adult in this survey have who also have a diagnosis of CLN2 Batten disease?

| | |
|---|---|
| 0 | 23 |
| 1 | 6 |
| 2 | 1 |
| 3 | 0 |



175) How old are these affected siblings (please select all that apply)?

| | |
|---|---|
| 0 | 4 |
| 1 - 2 | 0 |
| 3 - 4 | 1 |
| 5 - 6 | 3 |
| 7 - 8 | 1 |
| 9 - 10 | 1 |
| 11 - 12 | 1 |
| 13 - 14 | 0 |
| 15 - 16 | 0 |
| 17 – 18 | 0 |
| 18+ | 0 |



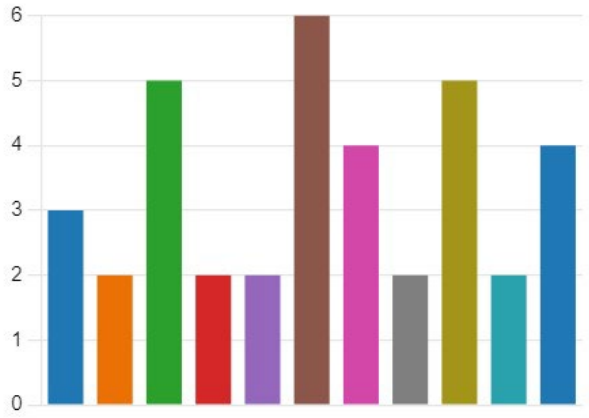

176) Are there any siblings that do not have CLN2 Batten disease?

| | |
|---|---|
| No | 4 |
| Yes, 1 | 17 |
| Yes, 2 | 3 |
| Yes, 3 | 2 |
| Yes, 4 | 3 |



177) How old are these unaffected siblings (please select all that apply)?

| | |
|---|---|
| 0 | 3 |
| 1 - 2 | 2 |
| 3 - 4 | 5 |
| 5 - 6 | 2 |
| 7 - 8 | 2 |
| 9 - 10 | 6 |
| 11 - 12 | 4 |
| 13 - 14 | 2 |
| 15 - 16 | 5 |
| 17 – 18 | 2 |
| 18+ | 4 |



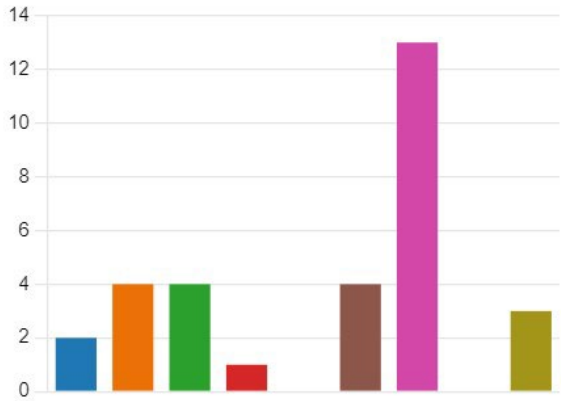

178) Do you think that caring for a child/children/young person(s)/younger adult(s) with CLN2 Batten disease has an impact on the physical health of their unaffected siblings?

| | |
|---|---|
| Yes | 14 |
| No | 13 |



179) Which of the following activities have had the greatest impact on the unaffected siblings' physical health (please select all that apply)?

| | |
|---|---|
| Physical lifting | 2 |
| Physical carrying | 4 |
| Feeding | 4 |
| Child/children/young person(s)/... | 1 |
| First aid/emergency care (e.g., s... | 0 |
| Lack of sleep | 4 |
| Lack of time | 13 |
| Other (please specify) | 0 |
| Other | 3 |




180) How would you rate the mental health of unaffected siblings?

| | |
|---|---|
| Very good | 5 |
| Quite good | 8 |
| Neither good nor poor | 10 |
| Quite poor | 1 |
| Very poor | 1 |



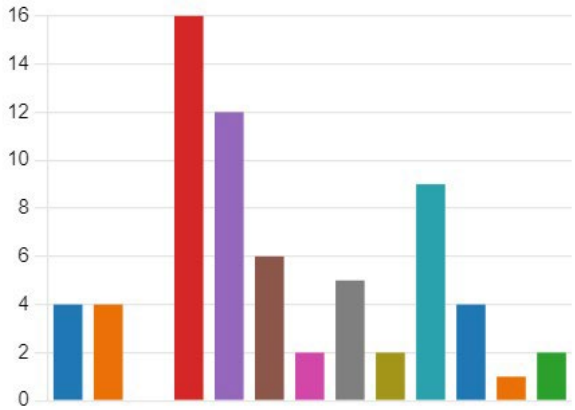
181) Do you think that caring for a child/children/young person(s)/younger adult(s) with CLN2 Batten disease has an impact on the unaffected siblings' mental health?

| | |
|---|---|
| Yes | 24 |
| No | 2 |



182) Which of the following have the greatest impact on the unaffected siblings' mental health (please select all that apply)?

| | |
|---|---|
| Lack of emotional support | 4 |
| Lack of physical support | 4 |
| Lack of suitable child/young per... | 0 |
| Uncertainty | 16 |
| Anxiety | 12 |
| Guilt | 6 |
| Depression | 2 |
| Adhering to the treatment timet... | 5 |
| Lack of sleep | 2 |
| Lack of personal time | 9 |
| Schooling | 4 |
| Other (please specify) | 1 |
| Other | 2 |




183) How would you rate the siblings' social wellbeing?

| | |
|---|---|
| Very good | 13 |
| Quite good | 8 |
| Neither good nor poor | 4 |
| Quite poor | 0 |
| Very poor | 0 |



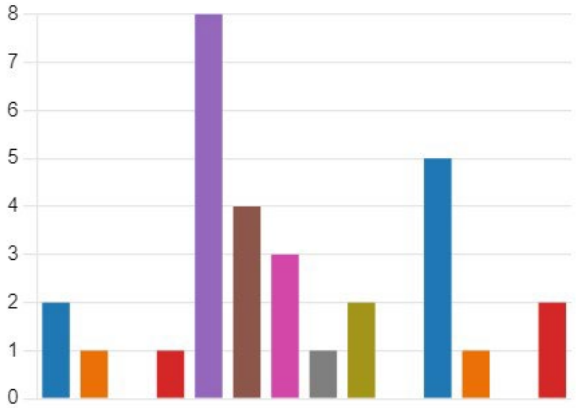
184) Do you think that caring for a child/children/young person(s)/younger adult(s) with CLN2 Batten disease has an impact on the siblings' social wellbeing (i.e., social isolation)?

| | |
|---|---|
| Yes | 10 |
| No | 15 |



185) Which of the following have the greatest impact on the unaffected siblings' social wellbeing?

| | |
|---|---|
| Lack of emotional support | 2 |
| Lack of financial support | 1 |
| Lack of physical support | 0 |
| Lack of suitable child/children/y... | 1 |
| Uncertainty | 8 |
| Anxiety | 4 |
| Guilt | 3 |
| Depression | 1 |
| Adhering to the treatment timet... | 2 |
| Lack of sleep | 0 |
| Lack of time | 5 |
| Transportation issues | 1 |
| Other (please specify) | 0 |
| Other | 2 |



186) Has caring for the child/young person/younger adult in this survey had any impact on the unaffected siblings' education? (please select all that apply)?

| | |
|---|---|
| Yes, a lot. | 2 |
| Yes, somewhat. | 4 |
| Yes, a little. | 6 |
| No | 10 |



187) Has caring for the child/young person/younger adult in this survey had an impact on the unaffected siblings' activities with friends?

| | |
|---|---|
| Yes, a lot. | 3 |
| Yes, somewhat. | 4 |
| Yes, a little. | 8 |
| No | 9 |



188) Has caring for the child/young person/younger adult in this survey had any impact on the unaffected siblings' family life?

| | |
|---|---|
| Yes, a lot. | 7 |
| Yes, somewhat. | 5 |
| Yes, a little. | 9 |
| No | 2 |



189) Please use the space below to tell us anything else about the impact CLN2 Batten disease has on their unaffected sibling(s). This should include information relating to the impact on individual siblings, for example older vs younger siblings if that is your family dynamic, that were not captured in this section.

| | |
|---|---|
| 1 | My eldest daughter has a diagnosis of autism and OCD, so some questions are not relevant as she has anxiety due to her autism and Beatrice isn't really that effected yet in terms of her CLN2 other than seizures |
| 2 | We try to give our child us much time with her friend us we can. |
| 3 | We have three children who do not have Batten Disease. Having a sibling with this disease affects each of our three children differently. Our oldest (16) really struggles, he has witnessed a lot before diagnosis which he can remember for example uncontrollable seizures. He also understands the importance of remaining on treatment and what will happen if the treatment is removed. He is a very sensitive person who worries a lot. Our middle child (15) is not affected at all, he takes everything as it comes, and it is not in his nature to worry. Our youngest (3) is too young to understand. She sees that her siblings are different however all she wants to do is help look after them. Having siblings with CNL2 Batten Disease is teaching her to be inclusive and caring towards others. We are parents worry that we have to split our time between all of our children. Our two children with Batten Disease do require more attention but we ensure our other children do not miss out. It does mean however sometimes we need to split up as a family to activities or we rely on others for help. |
| 4 | Although my son is 17 and quite self-sufficient, I don't feel I give him as much time. He has feelings of sadness a lot. |
| 5 | [redacted] sibling has learned to help and do caring for [redacted]. Anxiety has crept into [redacted] Sibling's life - however the school have really helped work this through with him. It affects his ability to concentrate, and he now has outbursts of rage and emotion. Even if emotion is due to an unrelated situation - it will then trigger sadness about [redacted]. |
| 6 | The time we have to spend with [redacted], not being able to do "normal" family activities, the constant care [redacted] requires, stress on the family, the uncertainty of the future |
| 7 | Our daughter has struggled with having a disabled brother. She is upset he is not cognitively aging and wishes he was able to be more active with her. She understands he needs more physical help and attention. We ensure we have regular conversations with her about the impact the disease and ensures she understands what is happening. Over the last 2 years she has become extremely caring and loving towards her brother. She loves to make him laugh and read hm stories. |
| 8 | Having a sibling with CLN2 means we cannot travel as freely and therefore are more dependent on having facility come visit us, which affects the sibling's time with other family. Being single parents also means it is harder to transport our unaffected son to his activities during the week and weekend. |

**PART 11**

**Other Issues/Comments**

190) This is a free section for you to add any information you feel is important that has not been covered in the survey.

| | |
|---|---|
| 1 | I'd like everyone to focus on what children can rather than what they can't. I'd like to say without BRINEURA they have no chance to live. Even though it might not work great deal or slow process of disease only little bit it's still life saving treatment. Without it all children would be dying rather than living full and happy lives |
| 2 | The lack of support for children with vision loss is massive. Children losing their vision lose confidence and skills. Some of these children are still cognitively aware that their vision is deteriorating. There is no physical, emotional, or educational support in place for these children or for parents. |
| 3 | We are new on the treatment schedule and early signs are positive. I worry that without treatment [redacted] would be on a much more apparent and quicker decline. The stabilisation we have seen so far is priceless for all those involved and for making future memories. We also know that in this early phase of treatment we are all still gathering new data which will be useful for future generations with this awful disease |
| 4 | Our child is not only learning new words but enjoying new experiences. She is enjoying new films (age related - Raya and the dragon). Finding new things she loves that we didn't know about. She LOVES all creative things. Our community nurse and local paediatrician have both cared for and treated battens children before and have both commented on the different patient that our child is because of Brineura. |
| 5 | I feel that without Brineura, our child may not be with us. |
| 6 | We lost our older daughter four weeks ago today (today's date is 20th November) due to severe complications with a chest infection. It was not because of Batten Disease). The anguish and heartbreak we are feeling cannot be put into words. We should have been completing this survey for both of our daughters and although our responses for our older sweetheart would have dramatically different to that of her younger sister, she still had the most wonderful life surrounded by love every second of every day. She had lost many of her abilities, but she could communicate in her own beautiful way. She radiated love and happiness, and we were blessed to have been her parents. We have always fought for our two daughters and now we continue the fight, but now it is for our youngest daughter, but never forgetting our angel. We will continue to do her proud and fight for what is right and what these poor children burdened with batten disease deserve. The treatment transformed her life and allowed her to enjoy a wonderful, amazing quality of life for being 11 years old with CLN2 battens. She enjoyed a multitude of activities at her amazing school which she attended full time, rebound on the trampoline, massage, sensory stories, sensory theatre groups, hydrotherapy and much more! We enjoyed family holidays to turkey (in September she was swimming in the Turkish sea and enjoying a Turkish hammam) Dubai, Disneyland Paris, Scotland, Rome, Yorkshire and lots of other places. We loved spending time at home, walking our dog and enjoying the simple pleasures. Although our daughter could not talk, she had a beautiful way of communicating and captured the hearts of everyone she met. She was one in a million and always followed her own special path. Brineura was amazing. It gave us |

| | |
|---|---|
| | years of beautiful memories and we had hoped for many more, but sadly this was not to be. We are lost with our darling girl, but we have to stay strong to fight to give her little sister, her best friend the chance to live a long life. We use our younger daughter to show the benefit of early diagnosis, in fact she is used around the world as an example of what is possible with early access to treatment. We had a comparison to show the difference a later diagnosis makes as our older daughter was fully dependant on us, but that did not diminish the right or the benefit of having treatment. She deserved it and she showed how transformative it is. The real and stark truth is children who are not on treatment aged 11 have either very sadly passed away or are in a palliative state. Aside from this acute health event which took our darling from us, she was in amazing health, and we expected to have many many more years with us. As we saw in our older daughter, quality of life should not be measured by how many steps a child can take or how many words they can say, or if they can count to ten. Our precious angel was proof of that. She couldn't do what her younger sister could do but she had just as much right and was benefiting amazingly well to the treatment. QOL is not as easy to quantify. It is about the child feeling loved and giving love by their presence. That is what we felt and what we gave to our sweetheart every day of her life. |
| 7 | I feel a lot of these questions assume there is only negativity around batten disease. Thanks to Brineura we have hope and the ability to keep our children healthy for longer. I had hoped some questions may have focused on the positive aspects of what Brineura has done for our son. Our son still loves to ride his trike, play with friends, play with his sister, swimming and so much more his quality of life is fantastic considering he had batten disease and I beg NICE to agree this treatment is worth every penny. |

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**PART 12**

**What Happens Next**

Thank you for completing this survey. Your responses will be a huge help to us to represent the voice of patients and carers.

We will use your response to inform the BDFA submission to any NICE appraisals for treatments for CLN2.

We will ensure that all data is anonymised.

All submissions made to NICE will be published on the BDFA website.

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**CLN2 Batten Disease Education Survey Introduction**

You have been asked to complete this survey because we understand that you have current involvement in the education of a child/young person/younger adult with a diagnosis of CLN2 Batten disease. Cerliponase alfa (Brineura) is a drug that is currently available as a treatment for the condition under a Managed Access Agreement with the NHS and its ongoing delivery is subject to a final approval by the National Institute for Health and Care Excellence (NICE).

The purpose of this survey is to gather relevant information to accurately fill in the patient advocacy form for submission to NICE as part of the re-evaluation of Brineura. As a patient advocacy group, the BDFA are charged with gathering data relating to the families' experiences of CLN2 and the treatment options available. During the resubmission process NICE will be looking at the clinical data gathered by the drug company BioMarin and the clinicians, but we contribute to the decisions made about treatments by sharing your voices and helping the committee to understand the real world, the lived experience of CLN2 Batten disease and Brineura. We are asking you to complete this questionnaire because you can provide valuable information about the life of an affected child/children/young person(s)/younger adult(s) in your school/college.

We recognise the emotional difficulty of adding comments in some of the "further information" sections of this questionnaire but, where appropriate, we would be grateful if you could complete those sections as they are often of great value to us in highlighting the real-life experiences of those contributing to the care, wellbeing, and education of young people with CLN2.

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**Confidentiality**

The survey and the data stored is completely anonymous. Once the report is created with the cumulative data, it will not be possible to identify any individual who submits answers. The survey questions, data, and report will be available to anyone once published on the NICE website hence the need for confidentiality.

The survey should be completed per child/children/young person(s)/younger adult(s). If you have more than one child/young person/younger adult with CLN2 Batten disease, please fill out a separate survey for that child/young person/younger adult. Please encourage anyone over the age of 18 years who has routinely interacts with the child/young person/younger adult in school to fill out the survey too, the more answers we have, the more accurate the data becomes.

Your participation in this survey is entirely voluntary and you ***do not have to answer any questions you do not want to***. We need your consent to process this information. If you are happy for us to use your information from this survey, please place a cross (X) the consent box below and confirm you are over the age of 18.

1) I consent to the information I provide by filling in this survey to be used by the BDFA.

2) I am over the age of 18 years.

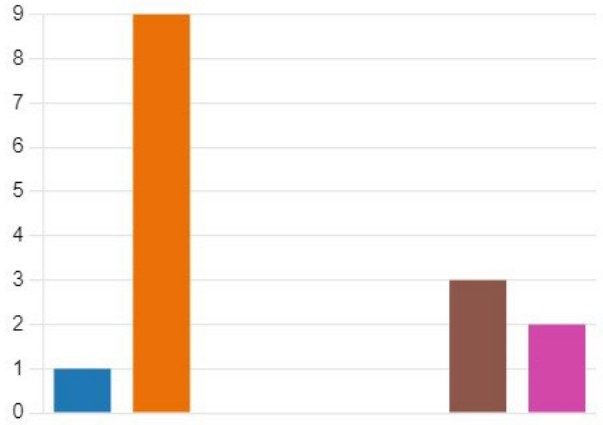
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**PART 1**

**About You**

3) What is the relationship between you and the child/children/young person(s)/younger adult(s) you are caring for?

| | |
|---|---|
| Head teacher | 1 |
| Class teacher | 9 |
| Nursery teacher | 0 |
| TA | 0 |
| SENCO | 0 |
| Other | 3 |
| Other | 2 |




4) Which geographical part of the UK do you live in?

| | |
|---|---|
| England | 12 |
| Northern Ireland | 1 |
| Scotland | 0 |
| Wales | 0 |



5) Is your school a mainstream school, a specialist school or a college?

| | |
|---|---|
| Mainstream | 1 |
| Specialist | 12 |
| College | 0 |



6) Name of educational establishment (anonymous)

**PART 2**

**The Patient**

7) Did you previously have child/children/young person(s)/younger adult(s) with a confirmed diagnosis of CLN2 Batten disease attend your school/college?

| | |
|---|---|
| Yes | 6 |
| No | 6 |



8) How many child/children/young person(s)/younger adult(s) with a confirmed diagnosis of CLN2 Batten disease have previously attended your school/college?

| | |
|---|---|
| One | 8 |
| Two | 0 |
| Three | 0 |



9) Do you currently have child/children/young person(s)/younger adult(s) with a confirmed diagnosis of CLN2 Batten disease attend your school/college?

| | |
|---|---|
| Yes | 11 |
| No | 2 |



10) How many child/children/young person(s)/younger adult(s) with a confirmed diagnosis of CLN2 Batten disease currently attend your school/college?

| | |
|---|---|
| One | 10 |
| Two | 2 |
| Three | 0 |



IMPORTANT NOTE: Please complete a separate survey for each affected child/children/young person(s)/younger adult(s) you care for.

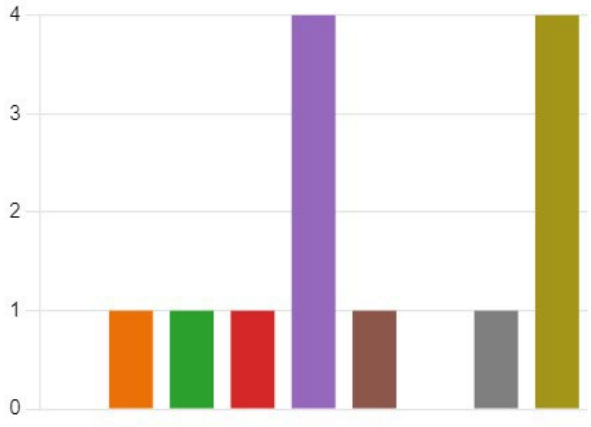
11) How old is the child/children/young person(s)/younger adult(s) you are completing this survey for?

| | |
|---|---|
| 0-3 years | 0 |
| 4-7 years | 6 |
| 8-11 years | 3 |
| 12+ years | 4 |



12) What age was the child/children/young person(s)/younger adult(s) in this survey when the CLN2 diagnosis was confirmed?

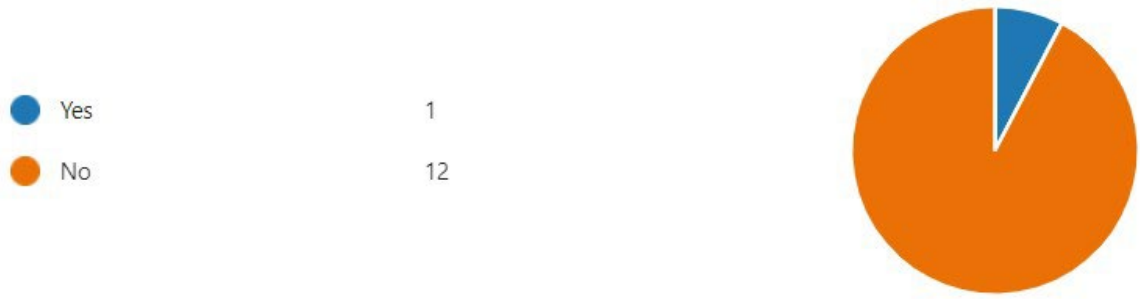
| | |
|---|---|
| 0 - <1 | 0 |
| 1 - <2 | 1 |
| 2 - <3 | 1 |
| 3 | 1 |
| 4 | 4 |
| 5 | 1 |
| 6 | 0 |
| 7+ | 1 |
| Don't know | 4 |



**PART 3**

**Diagnosis of CLN2**

13) Was the child/children/young person(s)/younger adult(s) in this survey at your school/college when they received their diagnosis?



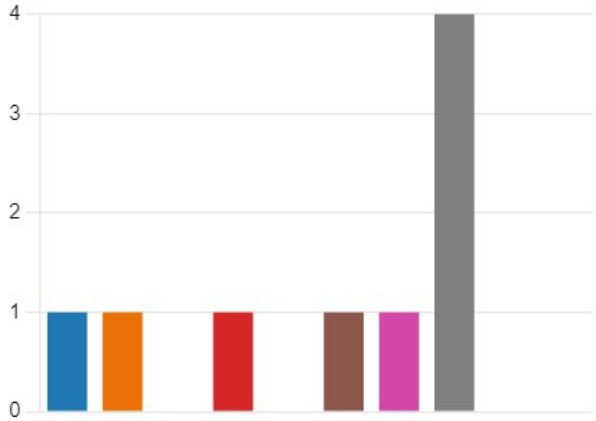

If your answer to question 1 was "yes", please complete questions 2 and 3 below, otherwise move to Part 4

14) Prior to the diagnosis, did you have any concerns about the development of the child/children/young person(s)/younger adult(s) in this survey that you discussed with their parents?



15) If your answer to question 14 was yes, which of the following did you flag?

| | |
|---|---|
| Seizures | 1 |
| Language delay | 1 |
| Delayed motor development | 0 |
| Issues with coordination, balanc... | 1 |
| Falls | 0 |
| Language development | 1 |
| Loss of motor skills | 1 |
| Not applicable | 4 |
| Other (please specify below) | 0 |
| Other | 0 |



**PART 4**

**School/College Life and Treatment**

16) For the child/children/young person(s)/younger adult(s) in this survey, how many days (on average) do they attend school/college?

| | |
|---|---|
| One | 0 |
| Two | 1 |
| Three | 0 |
| Four | 2 |
| Five | 10 |



17) For the child/children/young person(s)/younger adult(s) in this survey, how many hours per day (on average) do they attend school/college?

| | |
|---|---|
| 1 – 2 hours | 1 |
| 3 – 4 hours | 0 |
| 5 – 6 hours | 3 |
| Whole day | 9 |



18) For Q19 - Q25, where applicable, for the child/children/young person(s)/younger adult(s) in this survey, how are the following activities that they participate in during school/college hours been affected by having CLN2 Batten disease?

19) Ability to learn new skills

| | |
|---|---|
| Not affected | 0 |
| Slightly affected | 5 |
| Unable to retain information | 8 |



20) Playing with friends

| | |
|---|---|
| Not affected | 0 |
| Slightly affected | 8 |
| Unable to join in | 5 |



21) Playing games

| | |
|---|---|
| Not affected | 0 |
| Slightly affected | 6 |
| Unable to join in | 7 |



22) Imaginary play

| | |
|---|---|
| Not affected | 1 |
| Slightly affected | 5 |
| Unable to join in | 7 |



23) Self-care (for example, getting dressed)

| | |
|---|---|
| Not affected | 0 |
| Slightly affected | 5 |
| Unable to join in | 7 |



24) Eating and drinking

| | |
|---|---|
| Not affected | 0 |
| Slightly affected | 7 |
| Unable to join in | 6 |

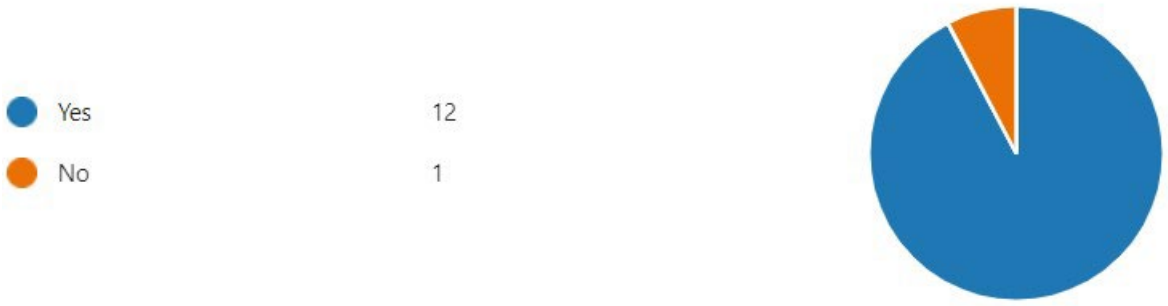


25) Other (please specify)




| | |
|---|---|
| 1 | The young man that we support in the home. He needs an individualised curriculum to enable him to use his residual senses to gain information from his environment. He needs clear and consistent routines and lots of repetition to anticipate what is happening next. He needs time to process information and cues to inform him. He is supported to be actively involved in the whole process of what he is doing using a Hand under Hand approach. He is responsive and able to play games through interaction. He shows enjoyment and will smile showing preferences. |
| 2 | Non-verbal, is fully assisted in everyday activities. |
| 3 | Slightly affected |
| 4 | Decline in coordination |
| 5 | Unable to join in |

26) Does the child/children/young person(s)/younger adult(s) in this survey suffer from fatigue that affects his or her ability to take part in these activities?



27) Does the child/children/young person(s)/younger adult(s) in this survey suffer from visual impairment that affects his or her ability to take part in these activities?

| | |
|---|---|
| Yes | 12 |
| No | 1 |



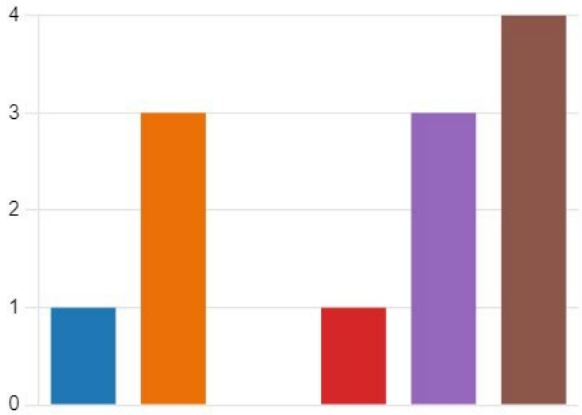
28) How does the child/children/young person(s)/younger adult(s) in this survey receive food and drink?

| | |
|---|---|
| Independently | 2 |
| With support | 5 |
| Gastrostomy fed | 6 |



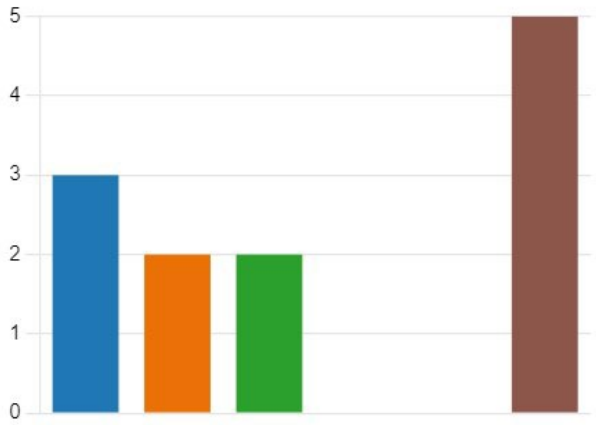
29) What type of diet was the child/children/young person(s)/younger adult(s) in this survey able to eat?

| | |
|---|---|
| Normal | 1 |
| Chopped | 3 |
| Finely chopped | 0 |
| Mashed | 1 |
| Blended | 3 |
| Enteral feeding (Gastrostomy or... | 4 |



30) What type of fluids was the child/children/young person(s)/younger adult(s) in this survey able to drink?

| | |
|---|---|
| Normal, unthickened | 3 |
| Grade 1 thickened | 2 |
| Grade 2 thickened | 2 |
| Grade 3 thickened | 0 |
| Grade 4 thickened | 0 |
| Fluids given enterally (Gastrosto... | 5 |




31) Is the child/children/young person(s)/younger adult(s) in this survey able to attend after school clubs?

| | |
|---|---|
| Yes | 4 |
| No | 9 |



32) Is the child/children/young person(s)/younger adult(s) able to attend local school outings and trips further afield?

| | |
|---|---|
| Yes | 10 |
| No | 3 |



33) How does the child/children/young person(s)/younger adult(s) in this survey use the toilet?

| | |
|---|---|
| Independently | 1 |
| With support | 1 |
| Uses pads (nappies) | 11 |



34) For Q35 - Q38, please answer whether the child/children/young person(s)/younger adult(s) in this survey has ever received any of the stated treatments at school?

35) Anti epilepsy drugs?

| | |
|---|---|
| Yes, currently | 8 |
| Yes, previously | 1 |
| No | 3 |



36) Sedatives?

| | |
|---|---|
| Yes, currently | 0 |
| Yes, previously | 1 |
| No | 11 |



37) Painkillers?

| | |
|---|---|
| Yes, currently | 4 |
| Yes, previously | 2 |
| No | 6 |



38) Other (please state the type of treatment(s) below)?

| | |
|---|---|
| Yes, currently | 0 |
| Yes, previously | 0 |
| No | 6 |
| Other | 4 |



| | |
|---|---|
| 1 | She has rescue medication but has never been used in school. |
| 2 | Has use of rescue medication when needed |
| 3 | Eye drops previously |
| 4 | Trihexphedidyl clonazepam |

39) For Q40 - Q48, please answer whether the child/children/young person(s)/younger adult(s) in this survey has ever required the use of the stated piece of equipment?

40) Wheelchair

| | |
|---|---|
| No | 1 |
| Yes, still using | 12 |
| Yes, no longer using | 0 |



41) Walker

| | |
|---|---|
| No | 4 |
| Yes, still using | 4 |
| Yes, no longer using | 5 |



42) Other walking aid

| | |
|---|---|
| No | 10 |
| Yes, still using | 1 |
| Yes, no longer using | 2 |

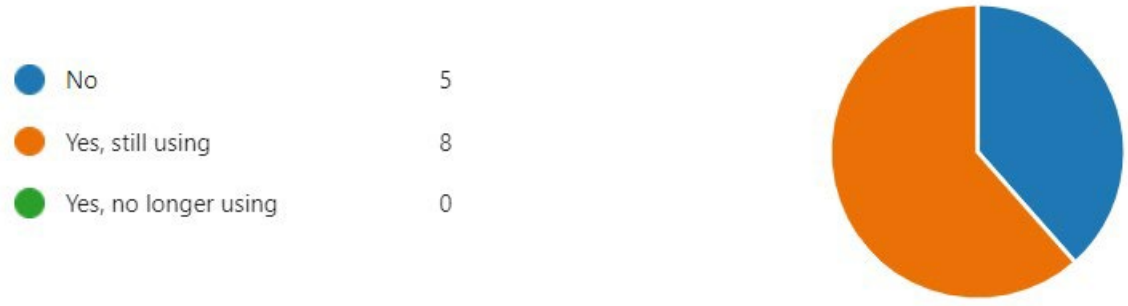


43) Hoist

| | |
|---|---|
| No | 4 |
| Yes, still using | 9 |
| Yes, no longer using | 0 |



44) Splints




45) Standing frame

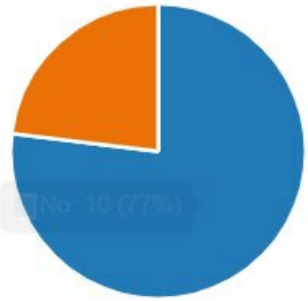



46) Beathing or ventilation support (e.g. suction, nebulisers, oxygen)



47) Visual aids (e.g Braille)

| | |
|---|---|
| No | 10 |
| Yes, still using | 3 |
| Yes, no longer using | 0 |



48) Communication device

| | |
|---|---|
| No | 7 |
| Yes, still using | 6 |
| Yes, no longer using | 0 |



49) Does/did the child/children/young person(s)/younger adult(s) in this survey receive(d) treatment with Brineura (cerliponase alfa)?

| | |
|---|---|
| No | 1 |
| No, currently waiting to start. | 0 |
| Yes, currently receiving treatment. | 12 |
| Yes, treatment discontinued. | 0 |



50) For Q51 - Q57, in comparison to your answers to Q19-Q25, if they receive Brineura, how are the following activities that the child/children/young person(s)/younger adult(s) in this survey participates in during school/college hours affected in the days leading up to an infusion day.

51) Ability to learn new skills

| | |
|---|---|
| Noticeably affected positively | 1 |
| Slightly affected positively | 0 |
| Not affected | 2 |
| Slightly affected negatively | 3 |
| Noticeably affected negatively | 6 |



52) Playing with friends

| | |
|---|---|
| Noticeably affected positively | 1 |
| Slightly affected positively | 0 |
| Not affected | 2 |
| Slightly affected negatively | 3 |
| Noticeably affected negatively | 6 |



53) Playing games

| | |
|---|---|
| Noticeably affected positively | 1 |
| Slightly affected positively | 0 |
| Not affected | 3 |
| Slightly affected negatively | 3 |
| Noticeably affected negatively | 5 |



54) Imaginary play

| | |
|---|---|
| Noticeably affected positively | 0 |
| Slightly affected positively | 1 |
| Not affected | 2 |
| Slightly affected negatively | 3 |
| Noticeably affected negatively | 5 |



55) Self-care (for example, getting dressed)

| | |
|---|---|
| Noticeably affected positively | 0 |
| Slightly affected positively | 1 |
| Not affected | 3 |
| Slightly affected negatively | 2 |
| Noticeably affected negatively | 6 |

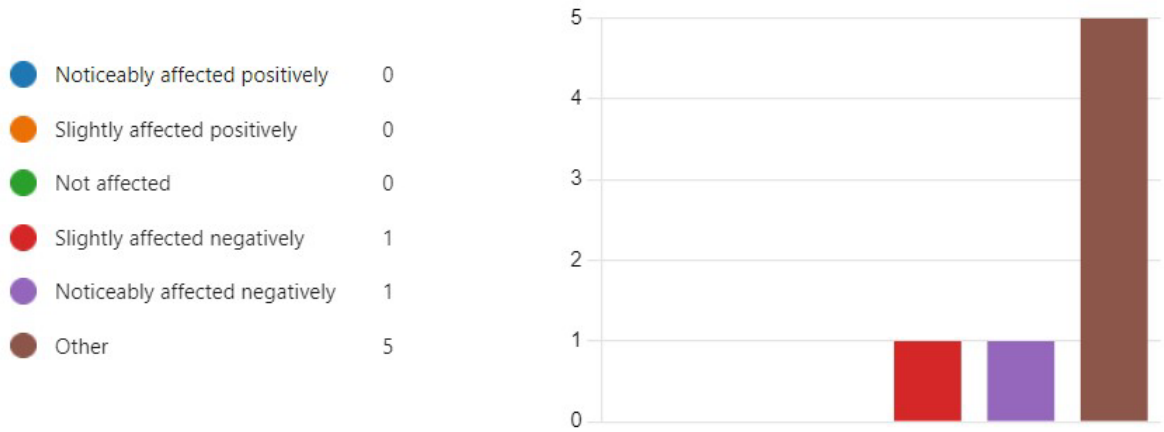


56) Eating and drinking

| | |
|---|---|
| Noticeably affected positively | 0 |
| Slightly affected positively | 1 |
| Not affected | 3 |
| Slightly affected negatively | 5 |
| Noticeably affected negatively | 3 |



57) Other (please specify)




| | |
|---|---|
| 1 | The learner we support is only a few hours a week |
| 2 | difficult to respond to questions 51 - 57 as young person doesn't have these skills anyway so remain unaffected for the positive or the negative. |
| 3 | happier in himself |
| 4 | Noticeably affected negatively |
| 5 | Very poor coordination |
| 6 | Slightly affected negatively |
| 7 | unable to help with any self care |

58) For Q59 - Q65, in comparison to your answers to Q19-Q25, if they receive Brineura, how are the following activities that the child/children/young person(s)/younger adult(s) in this survey participates in during school/college hours affected in the days following an infusion day.

59) Ability to learn new skills



60) Playing with friends

| | |
|---|---|
| Noticeably affected positively | 3 |
| Slightly affected positively | 2 |
| Not affected | 5 |
| Slightly affected negatively | 0 |
| Noticeably affected negatively | 3 |



61) Playing games

| | |
|---|---|
| Noticeably affected positively | 3 |
| Slightly affected positively | 3 |
| Not affected | 4 |
| Slightly affected negatively | 0 |
| Noticeably affected negatively | 3 |



62) Imaginary play

| | |
|---|---|
| Noticeably affected positively | 2 |
| Slightly affected positively | 3 |
| Not affected | 4 |
| Slightly affected negatively | 0 |
| Noticeably affected negatively | 3 |



63) Self-care (for example, getting dressed)

| | |
|---|---|
| Noticeably affected positively | 2 |
| Slightly affected positively | 2 |
| Not affected | 6 |
| Slightly affected negatively | 0 |
| Noticeably affected negatively | 3 |



64) Eating and drinking

| | |
|---|---|
| Noticeably affected positively | 2 |
| Slightly affected positively | 3 |
| Not affected | 5 |
| Slightly affected negatively | 1 |
| Noticeably affected negatively | 2 |



65) Other (please specify)

| | |
|---|---|
| Noticeably affected positively | 0 |
| Slightly affected positively | 1 |
| Not affected | 1 |
| Slightly affected negatively | 1 |
| Noticeably affected negatively | 0 |
| Other | 3 |



| | |
|---|---|
| 1 | We work with the individual for only a few hours a week. I couldn't say we notice a particular change but he can be tired - but as him family are with him all the time they may notice the changes in him after the infusions. We know that he can be tired but we don't particularly see this with him the next day when we see him and we are only with his for a short period. |
| 2 | As commented on, this person is fully assisted in everyday activities and events. Not clear about the question sorry. |
| 3 | Slightly affected positively |
| 4 | Coordination much better and controlled |
| 5 | Slightly affected negatively |
| 6 | Not affected |

66) In your opinion, is the behaviour of the child/children/young person(s)/younger adult(s) in this survey affected in the days leading up to an infusion day?




67) In your opinion, is the behaviour of the child/children/young person(s)/younger adult(s) in this survey affected in the days following an infusion day?



68) In your opinion, is the attention span of the child/children/young person(s)/younger adult(s) in this survey affected in the days leading up to an infusion day?




69) In your opinion, is the attention of the child/children/young person(s)/younger adult(s) in this survey affected in the days following an infusion day?




70) In response to your answers to Q51 – Q69, if you would like to, please use your own words to provide further information below.

| | |
|---|---|
| 1 | The learner we support has such complex and medical needs I couldn't say that if he was tired or struggling to focus was due to the medication. It may be because his muscles keep spasming and that is all he can focus on. Or he needs to change position, so he is showing this through his behaviour because this is how he communicates through his facial expressions, and body language. |
| 2 | Last Academic year, there was a really obvious regression in everything leading up to infusion. Especially tiredness and emotional regulation. Child was less chatty and independent. Once Infusion had occurred there was a really positive change in all areas. This year it is less obvious before and after, however there is still a change. |
| 3 | Prior to the infusion, this pupil is impacted greatly. They are unsettled, appear more distressed and less engaged in learning. The first day after the infusion, they are very tired |

| | |
|---|---|
| | but more relaxed. The few days after the infusion, they are very engaged, more excitable, more focused and alert in their learning. |
| 4 | This young person is fully assisted in all everyday activities and events, she remains the same with regards communication skills, physical movements etc. She is currently working on consolidating the skills she already has but is not in a position to learn new skills. She continues to have a go at anything with the right support and encouragement. |
| 5 | [redacted] is typically a happier and achieves more educational targets in school post treatment. |
| 6 | Seizure activity is almost daily in school, however their duration and occurrence is slightly reduced when they return to school after infusion. |
| 7 | Leading up to infusion day, we see a decline in physical abilities, both fine and gross motor. Also, definite change in behaviour; more outbursts, shouting, throwing, saying 'no'. Completely different child. |
| 8 | After discussions with Staff working with pupil, we have not observed any changes before or after. |
| 9 | Leading up to transfusion pupil can become tired more easily and find communication with adults hard. After treatment pupil is often a lot more chatty and alert and ready to learn. they also have more energy and seems to be more aware of and enjoy activities more. |

71) If you have experience of child/children/young person(s)/younger adult(s) with CLN2 Batten disease who attended before Brineura became available, have you noticed a difference between treated and untreated child/children/young person(s)/younger adult(s)ren?




72) If your answer to Q71 is yes, if you would like to, please use your own words to provide further information below.

| | |
|---|---|
| 1 | 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. |
| 2 | The pupil who attended our setting with CLN2, prior to Brineura being available, had a much shorter and more negatively impacted life. Their physical abilities reduced rapidly and they struggled with health and wellbeing. |
| 3 | Already on treatment when began attending our setting. |

73) Does receiving infusion treatment with Brineura mean the child/children/young person(s)/younger adult(s) in this survey misses more than one day of schooling each fortnight/per infusion?

| | |
|---|---|
| Yes | 4 |
| No | 9 |

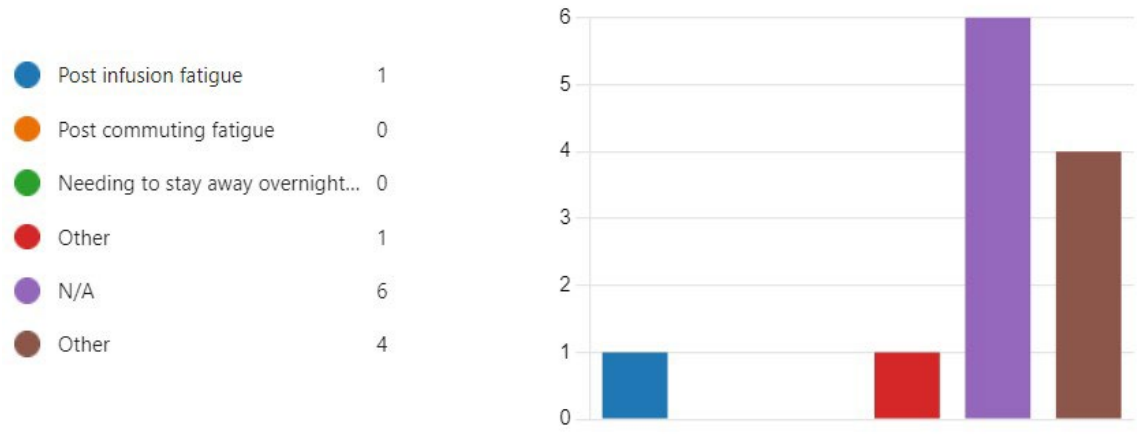


74) Does the child/children/young person(s)/younger adult(s) in this survey regularly miss more than one day of schooling due to treatment with Brineura?

| | |
|---|---|
| Yes, every time | 2 |
| Yes, frequently | 0 |
| Yes, infrequently | 1 |
| No | 10 |



75) Why does the child/children/young person(s)/younger adult(s) in this survey miss additional time?




76) In your opinion, does treatment with Brineura have an impact on the emotional well-being of the child/children/young person(s)/younger adult(s) in this survey?




77) In response to your answer to Q76, if you would like to, please use your own words to provide further information below.

| | |
|---|---|
| 1 | The learner we support is happy to engage with the familiar people around him especially his family. He loves laughter and hearing people laugh around him and will actively join in and smile. He can turn take with adults and shows interest in the world around him as long as it is made accessible to him ensuring that he is actively involved. He is a very happy child and enjoys the opportunities and experiences to learn. |
| 2 | The child has medical appointments in Bristol and swindon and with OT, Physio and Social Ot and wheelchair serves and splint clinics. |

| | |
|---|---|
| 3 | The pupil has a more relaxed and happy demeanour following treatment with Brineura. They regularly show signs of enjoyment and pleasure, with a beaming smile and excitable facial expression. They also appear more rested and less agitated. |
| 4 | After her treatment, she takes the next day to recover at home, being comfortable and making ready for her next day in school. She is not in a position to attend school the day after treatment. She would not then have the time to recover properly. |
| 5 | [redacted] is happier and more alert |
| 6 | it decreases seizure activity therefore helps with the general quality of life |
| 7 | Pupil has been consistently happy at school since epilepsy medication was stopped. |
| 8 | Pupil rarely misses school after treatment but if he does it means he needs to rest and generally benefits from having time to recouporate. We would rather this than be more tired in school and be more prone to seizures. |

**PART 5**

**Services**

78) For Q79 - Q85, as the child/children/young person(s)/younger adult(s) in this survey required the use of any of the following services during school/college hours?

79) Physiotherapist

| | |
|---|---|
| No | 1 |
| Yes, still using | 12 |
| Yes, no longer using | 0 |



80) Occupational therapist

| | |
|---|---|
| No | 1 |
| Yes, still using | 11 |
| Yes, no longer using | 1 |



81) Speech therapist

| | |
|---|---|
| No | 2 |
| Yes, still using | 11 |
| Yes, no longer using | 0 |



82) Dietician

| | |
|---|---|
| No | 4 |
| Yes, still using | 8 |
| Yes, no longer using | 0 |



83) QTVI

| | |
|---|---|
| No | 7 |
| Yes, still using | 5 |
| Yes, no longer using | 0 |



84) Music therapy

| | |
|---|---|
| No | 7 |
| Yes, still using | 5 |
| Yes, no longer using | 0 |



85) Other (please provide details below)

| | |
|---|---|
| No | 3 |
| Yes, still using | 1 |
| Yes, no longer using | 0 |
| Other | 4 |



86) Was it difficult to get any of these services?

| | |
|---|---|
| Yes | 3 |
| No | 9 |



**PART 6**

**Impact of COVID**

87) Do you feel that the COVID-19 pandemic had an impact on schooling for the child/children/young person(s)/younger adult(s) in this survey?




88) For Q89 - Q95, were any of the following services that were needed in your school/college for the child/children/young person(s)/younger adult(s) in this survey, affected during the COVID-19 pandemic?

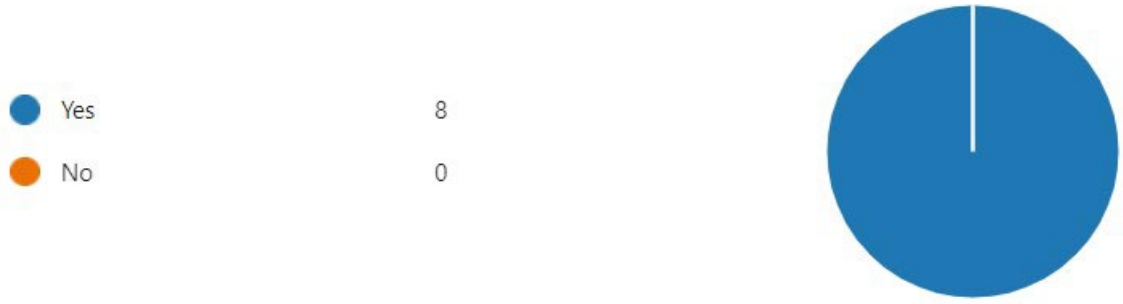
89) Physiotherapist



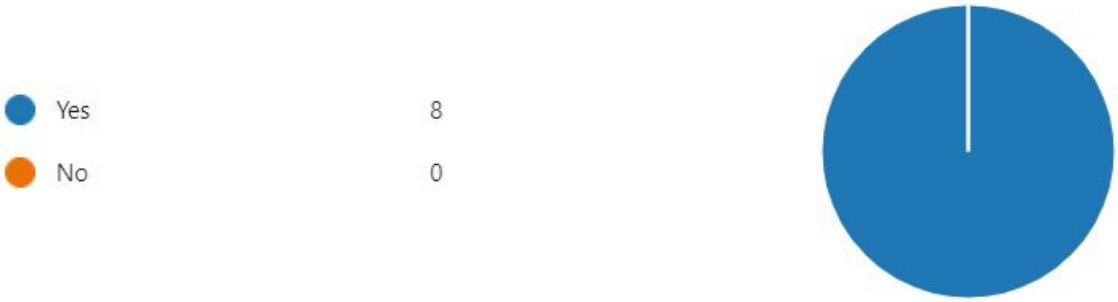
90) Occupational therapist




91) Speech therapist



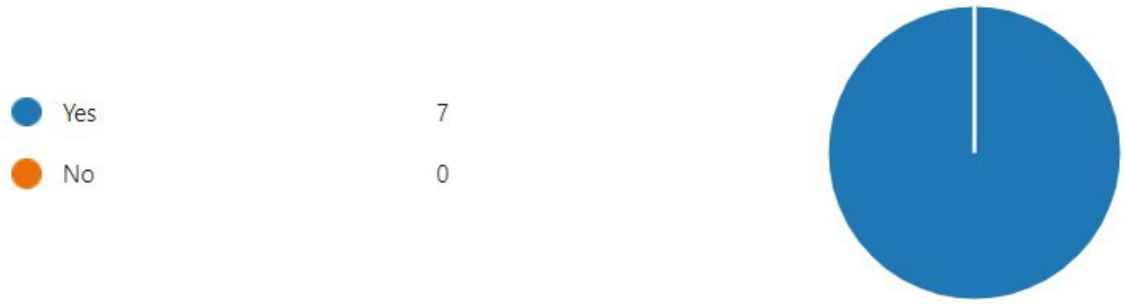

92) Dietician



93) QTVI




94) Music therapy




95) Other (please provide details below)




| | |
|---|---|
| 1 | All services did stop face to face as these learners were extremely vulnerable and so had to self-isolate. Sessions were available virtually but not always accessible for families this way. Physio and Hydrotherapy session weren't available due to self-isolating. |
| 2 | The whole school virtually closed down, no access to school therapists. |
| 3 | Child was not here during pandemic. |

96) Do you feel that the COVID-19 pandemic caused delay in accessing services needed to enable the child/children/young person(s)/younger adult(s) in this survey to attend school/college?




97) Please use your own words to describe the impact of the COVID-19 pandemic on the child/children/young person(s)/younger adult(s) in this survey.

| | |
|---|---|
| 1 | He was extremely vulnerable, and his family had to self-isolate to keep their family safe. He wasn't able to access any services during this time. This continued for quite some time until the family felt they could allow people into their home. |
| 2 | Child did not attend school during the pandemic. Enrolled in Mainstream school. |
| 3 | The pandemic limited regular and in person access to services required to support their health and wellbeing. It led to school being closed frequently, meaning the pupil could not get their regular interventions and pressure was put on the family at home to provide these instead. It took a long time for these services to 'return to normal' post-pandemic, which impacted the physical and health needs, such as equipment adjustment, regular therapies, and social interactions with others. |
| 4 | The young people were enrolled on home schooling. I sent packs home every week. Our parents, however, are not teachers they are parents. They did their very best and all the students returned to school after the pandemic with skills still intact. |
| 5 | initially all services were withdrawn but once school contact was reinstated the physiotherapy department fully engaged with children. |
| 6 | As the pupil was in our Early Years provision during the pandemic, due to school closures, she was unable to attend. |
| 7 | Pupil attended school after initial lock down |

**PART 7**

**Carer Information**

98) Do you think that having the child/children/young person(s)/younger adult(s) in this survey in your school/college has an impact on your physical health?




99) Do you think that having the child/children/young person(s)/younger adult(s) in this survey in your school/college has an impact on your mental health?




100) Has schooling for the child/children/young person(s)/younger adult(s) in this survey become more manageable since they started to receive Brineura?



101) Do you feel that you understand Batten disease and what it means for the child/children/young person(s)/younger adult(s) in this survey and their family?




102) Are you aware that child/children/young person(s)/younger adult(s) with CLN2 Batten disease require a holistic approach to maximise their ongoing treatment and quality of life?




103) Would your staff benefit from training to enable them to fully support a child/children/young person(s)/younger adult(s) with CLN2 Batten disease within your school/college?




104) If you have had previous experience with CLN2 Batten disease, has the introduction of Brineura changed your approach to having child/children/young person(s)/younger adult(s)in school/college who are on this treatment?

| | |
|---|---|
| Yes | 4 |
| No | 1 |
| Not applicable | 8 |



105) Please use the space below to tell us about your hopes and concerns about the child/children/young person(s)/younger adult(s) in this survey and their CLN2 Batten disease that have not been covered by the other questions.

| | |
|---|---|
| 1 | N/A |
| 2 | Many adults have limited knowledge on CLN2 Batten disease/Brineaura and the impacts/additional support required to help those with the diagnosis, as well as the impact on their families at home. There is limited support/information between settings who care for Batten's children, as well as support for declining health/ability. |
| 3 | I sincerely hope that this young person remains engaged, challenged, in an appropriate way, given plenty of opportunities to access different experiences. I need to be able to support both my young person and the adults surrounding her. I also think about, and sometimes worry about what comes next. This young lady is pushing boundaries, I think! I want to be in a position to understand what comes next and prepare my young lady, myself and my team in class. I want to be ready to be able to give the best support for my young lady and everyone around her. |
| 4 | Hope that [redacted] has a happy life and gets to enjoy the things he enjoys and that keeps him holistically well. |
| 5 | No knowing how quickly the disease will progress, especially with visual impairment and how we can manage this effectively. Also, the physical and cognitive impact of the disease. It would be helpful to have advice on the various stages and how we can support with this. |
| 6 | As a school we fully support treatment that can slow down symptoms that will reduce pupil's quality of life and overall enjoyment. Staff from pupil's current class notice how alert they can be after treatment. We all love having the pupil in class and love to see them smile and succeed. Their condition is ever changing and we staff are trained up to meet their needs. Pupil has adapted to learn in a multi-sensory way and this along with their Dystonia and seizure activity can exhaust them but we will do everything to support them and the family. Any training would be greatly appreciated. |

BATTEN DISEASE FAMILY ASSOCIATION
Together we WILL make a difference
Registered Charity In England and Wales 1084908 - Scotland SC047408

**PART 8**

**What Happens Next**

Thank you for completing this survey. Your responses will be a huge help to us to represent the voice of patients and carers.

We will use your response to inform the BDFA submission to any NICE appraisals for treatments for CLN2.

We will ensure that all data is anonymised.

All submissions made to NICE will be published on the BDFA website.

**MAA video links to YouTube**

https://youtube.com/playlist?list=PLfnx1BjHy3QOmV_uHnmXy7A2Bg335XLwO&si=h251Hl732P_N5nnf

https://www.itv.com/news/tyne-tees/2023-10-25/family-heartbroken-by-death-of-11-year-old-after-chest-infection

# CONFIDENTIAL UNTIL PUBLISHED
# External Assessment Group Report

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


| | |
|---|---|
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The authors have no competing interest to declare.

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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**Contributions of authors**

Ana Duarte performed the critical review of the economic analyses, wrote Sections 4, 5 and 6 of the report, validated the economic model, conducted the EAG additional analyses, led the overall economic analyses and took overall responsibility for the cost-effectiveness sections of the report (Sections 4, 5 and 6).

Anqian Zhou - performed the critical review of the economic analyses, conducted the EAG additional analyses, and contributed to drafting Sections 4, 5 and 6 of the report.

Mark Corbett contributed to all clinical sections of the report, and was primary author for section 3.

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Helen Fulbright provided information and library support, and assessed all review search strategies.

Natalia Kunst performed the critical review of the economic analysis, conducted the EAG additional analyses, contributed to drafting sections 4, 5 and 6 of the report, and provided technical support on the economic modelling.

Mark Simmonds contributed to all clinical sections of the report, and took overall responsibility for the clinical sections of the report (Sections 2 and 3).

**Note on the text**

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# List of abbreviations

| | | | |
|---|---|---|---|
| AE | Adverse event | NHS | National Health Service |
| AED | Anti-epileptic drug | NICE | National Institute for Health and Care Excellence |
| BNF | British National Formulary | NR | Not reported |
| CA | Cerliponase alfa | OCT | Optical coherence tomography |
| CADTH | Canadian Agency for drugs and Technologies in Health | PASS | Post-authorisation safety study |
| CeDR | Centre for Disability Research | PBAC | Pharmaceutical Benefits Advisory Committee |
| CEM | Company economic model | PedsQL | Paediatric Quality of Life Inventory |
| CEP | Cost effectiveness plane | PedsQL-FIM | Paediatric Quality of Life Inventory – Family Impact Module |
| CHO | Chinese hamster ovary | PfC | Points of clarification |
| CLN2 | Neuronal ceroid lipofuscinosis type 2 | PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| CLN2-QL | CLN2 quality of life | PRO | Patient reported outcome |
| CS | Company submission | PSS | Personal social services |
| CSF | Cerebrospinal fluid | PSSRU | Personal Social Services Research Unit |
| CSR | Clinical study report | QALY | Quality adjusted life year |
| EAG | External assessment group | QoL | Quality of Life |
| ECG | Electrocardiogram | RePEc | Research papers in economics |
| EEG | Electroencephalogram | SAE | Serious adverse event |
| EEPRU | Economic Evaluation of Health and Care Intervention | SD | Standard deviation |
| EMA | European Medicine Agency | SE | Standard error |
| eMIT | Electronic market information | SEN | Special educational needs |
| FAS | Full analysis set | SLR | Systematic literature review |
| FDA | Food and Drug Administration | SMC | Scottish Medicines Consortium |
| FU | Follow up | SmPC | Summary of products characteristics |
| GOSH | Great Ormond Street Hospital | SoC | Standard of care |
| HCHS | Hospital and Community Health Services | TBI | Traumatic brain injury |
| HR | Hazard ratio | TPP1 | Human Tripeptidyl peptidase 1 |
| HRQoL | Health Related Quality of Life | TRE | Temporally – related events |
| HS | Health State | UCL | Upper confidence level |
| HST | High Specialised Technology | UK | United Kingdom |
| HTA | Health Technology Assessment | US | United States |

| | |
|---|---|
| ICERs | Incremental cost-effectiveness ratios |
| ICV | Intracerebroventricular |
| INAHTA | International Health Technology Assessment Database |
| ITQoL | Infant Toddler Quality of Life Questionnaire™ |
| ITQoL97 | Infant Toddler Quality of Life Questionnaire™ 97-item full-length version |
| ITT | Intent-to-treat |
| IVT | Intravitreal |
| KM | Kaplan-Meier |
| LCL | Lower confidence level |
| LINCL | Late-infantile neuronal ceroid lipofuscinosis |
| MAA | Managed access agreement |
| MHRA | Medicines and Health Products Regulatory Agency |
| ML | Moor and Language |
| MLV | Motor, Language and Vision |
| MLVS | Motor, Language Vision, and Seizure |
| MRI | Magnetic resonance imaging |
| mUBDRS | Modified unified Batten disease rating scale |
| NA | Not applicable |
| NCPE | National Committee for Pharmacoeconomics |
| NH | Natural history |
| VA | Visual acuity |
| WISC-V | Wechsler Intelligence Scale for Children |
| WPPSI-IV | Wechsler Preschool and Primary Scale of intelligence |

# 1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

## *1.1 Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs compared to SoC by:

- Delaying disease progression and indirectly leading to life expectancy extension;
- Increased patient health state utility and lower caregiver/sibling disutility at each health state;
- Incurring disutility associated with adverse events (AEs).

Overall, the technology is modelled to affect costs by:

- Higher drug acquisition and administration costs;
- Higher health state costs;
- Incurring AE costs;
- Lower rates of progressive symptoms and annual number of seizures requiring rescue medication;
- Delay to vision loss for patients younger than 6 years;
- Higher residential costs.

The modelling assumptions that have the greatest effect on the ICER are:

- Evidence source used to inform the transition probabilities in health states 1-7;
- Baseline distribution of patients across health states;

- Whether vision loss progression for patients treated with cerliponase alfa is informed by i) disease progression with the SoC or ii) cerliponase alfa disease progression and age dependent vision loss;
- Treatment discontinuation for cerliponase alfa in health state 6 or 7;
- Magnitude of cerliponase alfa treatment effect on the patients' health state utilities.

## *1.2 Overview of the EAG's key issues*

**Table 1 Summary of key issues**

| ID6145 | Summary of issue | Report sections |
|---|---|---|
| 1 | Uncertain long-term trends in motor function and language | Section 3.3<br>Section 3.8 |
| 2 | Uncertainty as to whether benefits of cerliponase alfa vary with age or disease progression at treatment initiation | Section 3.3 |
| 3 | Uncertainty around benefits on seizure prevention | Sections 3.3 and 3.4.3 |
| 4 | Uncertainty around non-neurological effects, including myoclonus and dystonia | Sections 3.4.5 to 3.4.7 |
| 5 | Uncertain structural link between disease progression on motor and language domains, and other progressive symptoms | Sections 4.2.3, 4.2.7.3, 4.2.10 and 4.2.11.8 |
| 6 | Generalisability of company's preferred baseline distribution of patients across health states | Section 4.2.4 |
| 7 | Uncertainty around the initial stabilisation assumption | Section 4.2.7.1 |
| 8 | Appropriateness of evidence source informing transition probabilities in health states 1-7 | Section 4.2.7.1 |
| 9 | Robustness of transition probability estimates in health states 1-7 | Section 4.2.7.1 |
| 10 | Vision loss progression may not reflect natural history of disease | Section 4.2.7.4 |
| 11 | Cerliponase alfa treatment discontinuation rule is insufficiently justified | Section 4.2.8 |
| 12 | Uncertainty around treatment specific health state utilities | Section 4.2.10.3 |
| 13 | Appropriateness of excluding ECG monitoring costs for patients treated with cerliponase alfa | Section 4.2.11 |

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

1. EAG applied patient baseline characteristics as informed by the NICE committee's preference in the original HST12, while the company chose Study 190-203 (subgroup younger than 3) to inform these parameters;

2. EAG assumed that only 80% of patients treated with cerliponase alfa who enter the model in health state 1 are initial stabilisers, while the company preferred 100% of these patients were initial stabilisers;
3. EAG used the 'all patients' pooled dataset to inform transition probabilities in health states 1-7, while the company preferred to use data from Study 190-203 (subgroup younger than 3);
4. EAG assumed that vision loss for patients treated with cerliponase alfa occurred at the same rate as for patients treated with the standard of care (SoC) as informed by the NICE committee's preference in the original HST12, while the company modelled vision loss as partly dependent on age;
5. EAG assumed that patients are exposed to neuro-disability related mortality at all health states, while the company excluded this type of mortality from the model;
6. EAG assumed that treatment with cerliponase alfa stops when patients reach health state 7, while the company assumed this happened at health state 6;
7. EAG assumed that patients treated cerliponase alfa require ECG monitoring (with associated cost) for at least some infusions, while the company did not include this cost;
8. EAG assumed that patients in both treatment groups who are older than 13 years in health states 1-5 require psychiatric/behavioural support (with associated cost), while the company did not include this cost.

### *1.3 The decision problem: summary of the EAG's key issues*

The EAG did not identify any issues relating to the decision problem.

### *1.4 The clinical effectiveness evidence: summary of the EAG's key issues*

**Issue 1 Uncertain long-term trends in motor function and language**

| | |
|---|---|
| **Report section** | Sections 3.3 and 3.8 |
| **Description of issue and why the EAG has identified it as important** | While cerliponase alfa does appear to slow the progression of CLN2 disease the rate of decline may vary over time within patients, with possible long periods of stability and periods of rapid decline. The rate of progression may also be variable across patients. Rates of decline after long-term use (beyond 5 years), or at more severe stages of disease (ML score 1 or 2) is currently unclear. |
| **What alternative approach has the EAG suggested?** | No alternatives are possible at present |

| | |
|---|---|
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown. Transition probabilities in health states 1-7 assume continued treatment effect while patients remain on treatment with cerliponase alfa. |
| **What additional evidence or analyses might help to resolve this key issue?** | Continued long-term follow up of patients is required as disease progresses. |

**Issue 2 Uncertainty as to whether benefits of cerliponase alpha vary with age or disease progression at treatment initiation**

| | |
|---|---|
| **Report section** | Section 3.3 |
| **Description of issue and why the EAG has identified it as important** | There is some suggestion from the trials that patients who start treatment at younger ages (e.g. before age 3) and with limited disease progression (ML score of 6) might have a long period before disease progresses, or have slower disease progression. However, the number of patients with an ML score of 6 at treatment initiation is small, and most have limited follow-up, so their disease progression is uncertain. |
| **What alternative approach has the EAG suggested?** | No alternatives are possible at present. |
| **What is the expected effect on the cost-effectiveness estimates?** | This issue links to cost-effectiveness issues 7 and 8. |
| **What additional evidence or analyses might help to resolve this key issue?** | Further follow-up of patients who started treatment with an ML score of 6, and recruiting more of such patients to the MAA. |

**Issue 3 Uncertainty around benefits on seizure prevention**

| | |
|---|---|
| **Report section** | Sections 3.3 and 3.4.3 |
| **Description of issue and why the EAG has identified it as important** | Data from the CLN2 MLVS scale suggests that cerliponase alfa may be helping to prevent seizures or reduce their severity. However, this scale provides limited information on the clinical impact of seizures, and more detailed data on seizures was not available for most patients. Consequently, the true impact of any seizure prevention on quality of life is uncertain. |

| | |
|---|---|
| **What alternative approach has the EAG suggested?** | No alternatives are possible at present |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown, but company's base case suggests considerable cost-savings on seizure management for cerliponase alfa compared to SoC. |
| **What additional evidence or analyses might help to resolve this key issue?** | More detailed future collection of data on seizures including:<br>Number of seizures over time<br>Severity and type of seizures<br>Seizures needing hospitalisation |

**Issue 4 Uncertainty around non-neurological effects, including myoclonus and dystonia**

| | |
|---|---|
| **Report section** | Sections 3.4.5 to 3.4.7 |
| **Description of issue and why the EAG has identified it as important** | Evidence on non-neurological outcomes, such as myoclonus, dystonia, and cardiac events, and on quality of life generally, was very limited. If cerliponase alfa extends life, these non-neurological outcomes may have a greater impact on patient health and quality of life as they live longer. |
| **What alternative approach has the EAG suggested?** | No alternatives are possible at present |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown |
| **What additional evidence or analyses might help to resolve this key issue?** | Future collection of data on a broad range of outcomes beyond the MLVS scale is required. |

### *1.5 The cost-effectiveness evidence: summary of the EAG's key issues*

**Issue 5 Uncertain structural link between disease progression on motor and language domains, and other progressive symptoms**

| | |
|---|---|
| **Report section** | Section 4.2.3, Section 4.2.7.3, Section 4.2.10 and Section 4.2.11.8 |

| | |
|---|---|
| **Description of issue and why the EAG has identified it as important** | The disease progression is driven by changes to the combined motor and language score, which implicitly links progression on these domains directly to other key progression markers (developmental issues, seizures, requirement for a feeding tube, and palliative care). Due to this, observed clinical improvements and delay to progression as informed by the ML score result translate into impacts on other progression markers. The impact of the link between disease progression in terms of motor and language symptoms and progression in other disease symptoms not being established in this way, as well as the treatment effect of cerliponase alfa on the latter symptoms, are uncertain and difficult to validate, based on the evidence presented by the company. Furthermore, the treatment effect of cerliponase alfa on progressive symptoms is modelled in an inconsistent way between costs and health-related quality of life (HRQoL) impacts. Progressive symptoms resource use by health state and treatment is directly informed by elicited clinical opinion, while the impact of these symptoms on patient HRQoL is not. Instead, progressive symptoms as described in health state vignettes are captured into the treatment specific health state utilities informed by a published study.[1] The description of progressive symptoms in the vignettes does not completely align with the elicited progressive symptoms resource use.<br>The model structure has previously been accepted by the NICE committee's to the original HST12, as appropriate to inform decision making. However, the EAG considers that the decision uncertainty associated with this structural feature has increased by applying additional (within health state) treatment effects for cerliponase alfa vs. SOC on progressive symptoms in this re-appraisal. |
| **What alternative approach has the EAG suggested?** | Use primary data collected for cerliponase alfa since the last appraisal to validate the impact on progressive symptoms of cerliponase alfa by health state. This evidence is unlikely to be comparative vs. SoC, but could be used to inform the cerliponase alfa treatment group resource use (SoC resource use could then |

| | |
|---|---|
| | be elicited). Furthermore, these primary data could also be used to validate the existing vignette study and/or inform a new one. |
| **What is the expected effect on the cost-effectiveness estimates?** | The EAG explored the impact of cerliponase alfa having no (within health state) treatment effect on the proportion of patients incurring the costs of progressive symptoms (other than seizures) vs. SoC. Depending on whether these parameters were informed by cerliponase alfa or SoC estimates, the ICER was [redacted] and [redacted] per additional QALY, respectively. The company's base-case ICER was [redacted] per additional QALY The impact of overestimating impacts on HRQoL is unknown. |
| **What additional evidence or analyses might help to resolve this key issue?** | Please see "What alternative approach has the EAG suggested?" |

**Issue 6 Generalisability of company's preferred baseline distribution of patients across health states**

| | |
|---|---|
| **Report section** | Section 4.2.4 |
| **Description of issue and why the EAG has identified it as important** | The baseline distribution of patients across health states should reflect that of patients initiating treatment in clinical practice and depends on how progressed disease is at the point of diagnose. There is an expectation that diagnosis will occur earlier in disease progression (and patient age) in the future, but how early is an area of uncertainty. The baseline distribution of patients in the model is a key cost-effectiveness driver (particularly due to the initial stabilisation assumption – see Issue 7) and area of uncertainty. Company's preferred distribution may be overly skewed towards higher ML scores given current and future clinical practice, according to clinical advice received by the EAG. |
| **What alternative approach has the EAG suggested?** | The EAG preferred approach is to apply the same baseline distribution as preferred by the NICE committee's for the original appraisal. However, the EAG notes that this distribution was still considered optimistic by the clinical adviser to the EAG. |

| | |
|---|---|
| **What is the expected effect on the cost-effectiveness estimates?** | Under the EAG's preferred assumptions, the ICER for cerliponase alfa vs. SoC increase from [redacted] to [redacted] per additional QALY compared to the company's base-case. The baseline distributions suggested by the clinical adviser as reflective of patients in current clinical practice and in 5-year time resulted in ICERs of [redacted] and [redacted] per additional QALY, respectively. |
| **What additional evidence or analyses might help to resolve this key issue?** | Additional clinical opinion could be sought to improve the generalisability of these parameters to NHS practice. |

**Issue 7 Uncertainty around the initial stabilisation assumption**

| | |
|---|---|
| **Report section** | Section 4.2.7.1 |
| **Description of issue and why the EAG has identified it as important** | The company assumed that the proportion of patients who enter the model in health state 1 (ML score 6) are initial stabilisers and all remain in health state 1 (unless they die or discontinue treatment) for the first 6 years in the model. Beyond 6 years, the transitions in health states 1 to 7 for stabilisers occur at half the rate of the transition probabilities applied to those who enter the model in the remaining health states (i.e., non-stabilisers). This assumption was informed by observations in a small number of patients and over a follow-up not greater than 6 months for the majority of patients. As noted in issue 2, it is also uncertain whether lack of disease progression by initial stabilisers is due to solely to cerliponase alfa or is also a function of age. Initial stabilisation assumption for patients treated with cerliponase alfa is highly uncertain and may be a driver of cost-effectiveness (particularly when the baseline distribution of patients concentrates on health state 1) despite the additional evidence generated since original HST12 and more conservative assumptions have not been explored by the company. |
| **What alternative approach has the EAG suggested?** | The EAG preferred to assume that only 80% of patients who enter the model at health state 1 are initial stabilisers, as suggested by clinical advice to the EAG. |

| | |
|---|---|
| | The EAG also explored the impact of modifying the rate of progression beyond 6 years using more conservative assumptions than the company's. |
| **What is the expected effect on the cost-effectiveness estimates?** | Under the EAG's preferred assumption, the ICER for cerliponase alfa vs. SoC increases from [redacted] to [redacted] per additional QALY compared to the company's base-case. When considering more conservative assumptions for the initial stabilisers rate of progression beyond 6 years the resulting ICERs ranged between [redacted] and [redacted] per additional QALY, respectively. |
| **What additional evidence or analyses might help to resolve this key issue?** | Further follow-up of patients who started treatment with an ML score of 6 and collect data on higher number of such patients. |

**Issue 8 Appropriateness of evidence source informing transition probabilities in health states 1-7**

| | |
|---|---|
| **Report section** | Section 4.2.7.1 |
| **Description of issue and why the EAG has identified it as important** | The company's preferred evidence source to inform the transition probabilities in health states 1 to 7 for patients treated with cerliponase alfa, Study 190-203, may not reflect the population in current and near future clinical practice and be overestimate treatment effectiveness of the technology. Furthermore, Study 190-203 has a smaller sample size and fewer number of events to inform transition probabilities than the 'all patient' dataset. The EAG considers that the 'all patients' pooled dataset (matched to Study 190-901) is the most appropriate source of evidence to inform the transition probabilities in health states 1-7, because this source reflects the majority of existing evidence for these parameters due to sample size and overall length of follow-up. |
| **What alternative approach has the EAG suggested?** | Use 'all patients' pooled dataset (matched to Study 190-901) to inform the transition probabilities in health states 1-7. |
| **What is the expected effect on the cost-effectiveness estimates?** | Under the EAG's preferred assumption, the ICER for cerliponase alfa vs. SoC increases from [redacted] to [redacted] per additional QALY compared to the company's base-case. |

| | |
|---|---|
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG considers their preferred data source to be the most appropriate unless further data cuts of ongoing studies can be used to supplement it. |

**Issue 9 Robustness of transition probability estimates in health states 1-7**

| | |
|---|---|
| **Report section** | Section 4.2.7.1 |
| **Description of issue and why the EAG has identified it as important** | The EAG cannot establish whether the statistic model applied to estimate the transition probabilities for health states 1-7 provides robust estimates for the transition probabilities applied in the model, due to the unclear impact of using arbitrary initial values to inform the MSM models and the potential overfitting of these models to the observed data. Furthermore, the company did not test alternative estimation methods for these transition probabilities (e.g., different statistical methods and/or aggregation of health states), which contributes to the uncertainty around the robustness of these parameters. |
| **What alternative approach has the EAG suggested?** | The EAG 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 on the derived transition probabilities and/or statistical model goodness of fit. This could not be explored by the EAG with the data provided by the company. The EAG did explore an extreme scenario whereby the impact of applying a restriction to the cerliponase alfa transition probabilities for patients in health state 1-7 so that transitions to previous healthier states are not possible. |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown. Under the restrictions of the scenario not allowing backward transitions to healthier states for both treatments the ICER for cerliponase alfa vs. SoC increases from [redacted] to [redacted] per additional QALY compared to the company's base-case. |
| **What additional evidence or analyses might help to resolve this key issue?** | Analysis with alternative estimates for transition probabilities using alternative i) sets of initial values, ii) statistical approaches, and iii) level of health state aggregation (e.g., as per original HST12), may allow defining the potential impact of this uncertainty on the estimates of cost-effectiveness. |

**Issue 10 Vision loss progression may not reflect natural history of disease**

| | |
|---|---|
| **Report section** | Section 4.2.7.4 |
| **Description of issue and why the EAG has identified it as important** | The company's approach to modelling progression of vision loss with age may not reflect the natural disease progression and favour the cost-effectiveness of cerliponase alfa, based on clinical opinion received by the EAG. |
| **What alternative approach has the EAG suggested?** | Model vision loss as per NICE committee's preference for the original appraisal. |
| **What is the expected effect on the cost-effectiveness estimates?** | Under the EAG's preferred assumption, the ICER for cerliponase alfa vs. SoC increases from [redacted] to [redacted] per additional QALY compared to the company's base-case. A scenario modelling this assumption as per the company base-case, but assuming that vision loss associated with age occurs between 6 and 10 years (instead of between 6 and 20 years) results in an ICER of [redacted] per additional QALY. |
| **What additional evidence or analyses might help to resolve this key issue?** | Seek further clinical opinion to inform the assumptions around vision loss. |

**Issue 11 Cerliponase alfa treatment discontinuation rule is insufficiently justified**

| | |
|---|---|
| **Report section** | Section 4.2.8 |
| **Description of issue and why the EAG has identified it as important** | The company's base-case assumption on treatment discontinuation is insufficiently justified by existing evidence and may disproportionally favour the cost-effectiveness of cerliponase alfa compared to SoC due to how the stopping rule was implemented in the economic model. The model implementation of this feature implies a persistence of treatment effect of cerliponase alfa on transition probabilities from health state 6 that is potentially too optimistic according to clinical advice received by the EAG. |

| | |
|---|---|
| **What alternative approach has the EAG suggested?** | Assume treatment discontinuation at health state 7 as per the original HST12. |
| **What is the expected effect on the cost-effectiveness estimates?** | Under the EAG's preferred assumption, the ICER for cerliponase alfa vs. SoC increases from [redacted] to [redacted] per additional QALY compared to the company's base-case. |
| **What additional evidence or analyses might help to resolve this key issue?** | Clinical opinion on what stopping rule is likely to be used in clinical practice.<br>The economic model may have to be adapted to incorporate less favourable assumptions on treatment effect maintenance once treatment is stopped. |

**Issue 12 Uncertainty around treatment specific health state utilities**

| | |
|---|---|
| **Report section** | Section 4.2.10.3 |
| **Description of issue and why the EAG has identified it as important** | While the Gissen et al., 2021, study[1] is the only study reporting comparative health state utilities for cerliponase alfa and the SoC, it is affected by considerable uncertainty and the derived utility estimates may be affected by bias. The patient's health state utilities and the magnitude of the cerliponase alfa treatment effect on health state utilities is an important area of uncertainty |
| **What alternative approach has the EAG suggested?** | None – to the EAG's best knowledge there is no other alternative source of comparative evidence on health state utilities for cerliponase alfa vs. SoC. |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown, but potentially large. Under the company's scenario assuming that patient's health state utilities are treatment independent, the ICER for cerliponase alfa vs. SoC ranges from [redacted] per additional QALY, which is higher than the company's base-case ICER ([redacted] per additional QALY) |
| **What additional evidence or analyses might help to resolve this key issue?** | Alternative source of comparative evidence on patient's health state utilities for cerliponase alfa vs. SoC. |

**Issue 13 Appropriateness of excluding ECG monitoring costs for patients treated with cerliponase alfa**

| | |
|---|---|
| **Report section** | Section 4.2.11 |
| **Description of issue and why the EAG has identified it as important** | The company's exclusion of the costs associated with ECG monitoring of patients during infusion of cerliponase alfa is not in line with the drug's SmPC and the NICE committee preferences in the original HST12. This exclusion was not justified and is likely to underestimate the cost of administering cerliponase alfa, as the information reported in the CS does not allow identifying the proportion of patients who have had at least one prior ECG clinically significant result and furthermore, not all patients had a 42 weeks follow-up. Thus, the estimates of resource use applied by the EAG are an approximation. |
| **What alternative approach has the EAG suggested?** | Include these costs. |
| **What is the expected effect on the cost-effectiveness estimates?** | Under the EAG's preferred assumption, the ICER for cerliponase alfa vs. SoC increases from [redacted] to [redacted] per additional QALY compared to the company's base-case. The EAG notes that this is a potential underestimation of the costs associated with ECG monitoring |
| **What additional evidence or analyses might help to resolve this key issue?** | Better information on proportion of patients clinically significant ECG results at baseline and cumulatively over time. |

## *1.6 Other key issues: summary of the EAG's view*

None

### *1.7 Summary of EAG's preferred assumptions and resulting ICER*

**Table 2 Deterministic cost-effectiveness results for the EAG's preferred assumptions**

| Scenario | Incremental cost | Incremental QALYs | ICER (change from company base case) | CE threshold* £/QALY |
|---|---|---|---|---|
| Company's base case | [redacted] | 17.35 | [redacted] | |
| Baseline characteristics as per original HST12 | [redacted] | 13.84 | [redacted] | £271,374 |
| 80% of patients in HS1 are initial stabilisers | [redacted] | 16.30 | [redacted] | £300,000 |
| Transition probabilities health state 1-7 informed by 'all patient dataset' | [redacted] | 14.27 | [redacted] | £246,232 |
| Vision loss as per original HST12 | [redacted] | 16.45 | [redacted] | £300,000 |
| Neuro-disability mortality applies to HS1-9 | [redacted] | 17.31 | [redacted] | £300,000 |
| Treatment discontinuation at HS7 | [redacted] | 17.79 | [redacted] | £300,000 |
| Including ECG costs | [redacted] | 17.35 | [redacted] | £300,000 |
| Including psychiatric/behavioural support costs | [redacted] | 17.35 | [redacted] | £300,000 |
| EAG's preferred base case | [redacted] | 9.91 | [redacted] | £169,561 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC. Abbreviations: CE, cost-effectiveness; ECG, electrocardiogram; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.

# EXTERNAL ASSESSMENT GROUP REPORT

## 2 INTRODUCTION AND BACKGROUND

### *2.1 Introduction*

This report presents a critique of the company's submission (CS) to National Institute for Health and Care Excellence (NICE) from BioMarin Limited on the clinical effectiveness and cost effectiveness of cerliponase alfa (Brineura®) for treating neuronal ceroid lipofuscinosis type 2 (CLN2).

Cerliponase alfa received a full marketing authorisation throughout the EU, granted by the European Medicines Agency (EMA) on 30th May 2017. [2] The Medicines and Health products Regulatory agency (MHRA) further granted a marketing authorization for cerliponase alfa under the managed access agreement (MAA) for treating patients with CLN2 [3] on 1st January 2021.

This report represents an update and new review of cerliponase alfa subsequent to an original submission from BioMarin Limited in December 2017 as part of appraisal 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 [4] (see CS section B.2.3.3).

Since HST12 new evidence has emerged. This includes long-term effectiveness data from study 190-202 [5-7] (which is an extension of study 190-201 [8-10]); new sources of clinical effectiveness evidence from the MAA and from study 190-203; [11, 12] three long term safety studies (study 109-501, [13] study 109-502,[14] and study 109-504 [14]); and two supplementary studies (190-801 and DEM-CHILD-RX). Consequently, cerliponase alfa is being reviewed again. This EAG report, considers all the evidence submitted by the company in January 2024, focusing on the new evidence generated since the previous assessment.

## *2.2 Background*

### 2.2.1 Neuronal Ceroid Lipofuscinosis type 2 (CLN2):

The company's description of CLN2 is broadly appropriate and relevant to the decision problem. This is presented in section B.1.3.1 of the company submission (CS). The EAG presents a broad summary of the disease and its treatment here.

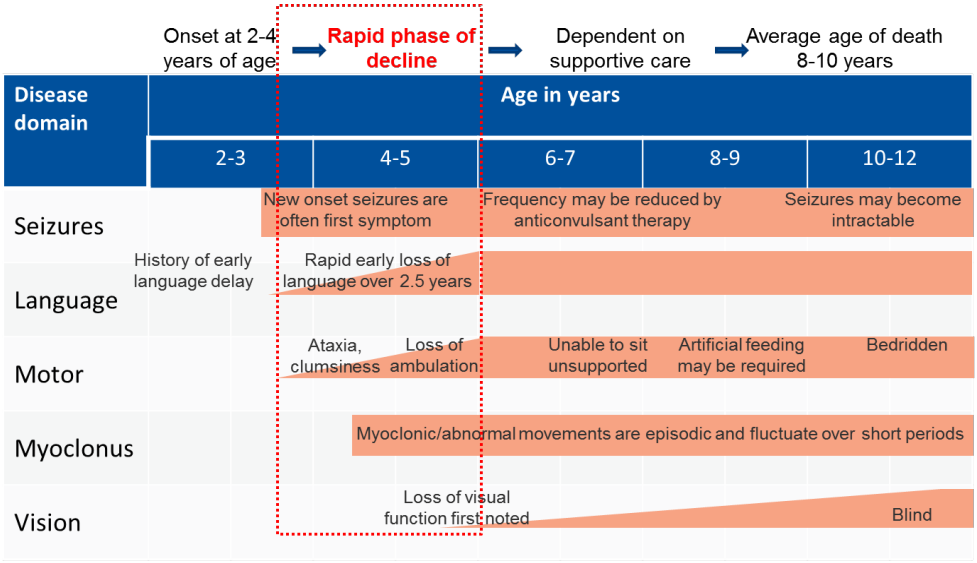
CLN2 is an ultra-rare progressive, inherited neurodegenerative disease that is primarily caused by pathogenic variants in the TPP1/CLN2 gene leading to the deficient activity of lysosomal enzyme (TPP1 [15, 16]). It is characterised by motor deterioration, speech or language delay, seizure, ataxia, dementia, loss of vision and ultimately, early death[17].

There are two forms of CLN2: typical and atypical. Typical CLN2 manifests usually between ages 2 and 4 and has a rapid progression rate and early mortality. Death typically occurs between age 8 and early adolescence. [16, 18] Atypical CLN2 has later onset of symptoms (between 6 and 8 years, based on clinical advice to the EAG), a prolonged disease course and longer life expectancy. The CS stated that atypical CLN2 affects approximately 10% of CLN2 patients, a prevalence which the EAG's adviser agreed with

The exact prevalence of CLN2 in the UK is unknown because of its rarity; the company estimated that there are about 40 CLN2 patients currently in England. This is broadly in line with advice given to the EAG of approximately 50 patients in the UK. As of September 2023, there are 35 CLN2 patients who have received cerliponase alfa under the MAA, of which 26 new patients were enrolled between November 2019 and September 2023.

The typical course of the disease progression, as described in the CS (presented in Figure 1) is accurate. Most CLN2 patients present with an onset seizure or ataxia with history of speech or language delay, which progresses to a deterioration in motor functionality, severe seizures, loss of vision and ultimately early death.

**Figure 1 Typical Course pf CLN2 disease [CS Figure 1]**




### 2.2.2 Burden of disease

The company's description of the burden of CLN2 (reported in section B.1.3.4 of the CS) is broadly appropriate and relevant to the decision problem. This included: clinical burden on patients, including mortality; the quality-of-life burden on patients; impact on caregivers and families; impact on education; financial burden, and economic burden.

According to the company, prior to the availability of cerliponase alfa, patients were prescribed many medications to manage the various symptoms like seizures, dystonia, mood change and vision loss. [19] Patients needed supportive care from wide range of medical professionals including neurologists, cardiologist, speech therapists, and a palliative care team. Patients and their caregivers had to travel to one of the few centres with capacity to treat the condition. The average age of death for untreated CLN2 patients was between 8 and 12 years. [18, 20-22] There is a consequent, substantial quality-of-life burden on parents, caregivers, and families. A US study showed that the HRQoL of CLN2 patients was very poor relative to the US general population in all the domains except for "family cohesion" and "bodily pain / discomfort".

The caregivers and families of CLN2 patients reported that the burden due to CLN2 is overwhelming and impacts substantially on family life. Caregivers reported that caring for a child with CLN2 disease is like "a full-time job of three people. [19] In addition, they experience anxiety, sleep disruption, back pain due to carrying the affected child and physical exhaustion. Siblings of CLN2 patients experience similar issues. Families often have to give up work to take care of an affected child. The high cost of acquiring necessary equipment like specialist wheelchairs, and home installation of hoists and ramps to take care of the affected further increases the financial burden due to CLN2 disease. [23]

### 2.2.3 Cerliponase alfa

The company's description of the technology, cerliponase alfa, is broadly clear and appropriate.

Cerliponase alfa is a recombinant form of human tripeptidyl peptidase (TPP1) produced in mammalian Chinese hamster ovary (CHO) cells. It is the only treatment to target the cause of CLN2; that is, the deficiency of TPP1. It is an enzyme replacement therapy which is administered every other week at 300mg per dose for children aged 2 years and above. For children below 2 years the dose varies depending on their age. Cerliponase alfa is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted intracerebroventricular (ICV) infusion access device (reservoir and catheter).

The treatment must be administered in specialised health care settings (also known as CLN2 clinics in UK) by trained practitioners. Currently, there are six centres in the England: Great Ormond Street Hospital (GOSH) in London; Birmingham Children's Hospital; Bristol Royal Hospital for Children; Manchester University Hospital; Royal Victoria Infirmary in Newcastle, and Salford Royal Hospital.

### 2.2.4 Clinical pathway

The clinical pathway described in section B.1.3.5 of the CS broadly reflects the current UK practice for the management of CLN2. There are currently no UK national guidelines or guidance in place for the management of CLN2 disease.

#### *2.2.4.1 Diagnosis*

Diagnosis of CLN2 is primarily based on laboratory enzyme testing for deficiency of TPP1. This test is performed in infants or children presenting with onset seizures, or with delayed speech. Enzyme testing will also be performed in infants with affected siblings, or where parents or relatives are known to carry the mutations in the TPP1/CLN2 gene.

The company highlighted that diagnosis may be delayed due to a general lack of awareness of CLN2 among clinical practitioners and consequent misinterpretation of symptoms. The EAG's clinical adviser noted that there is now increased awareness of CLN2 and the availability of cerliponase alfa. Patients with CLN2 may therefore be increasingly diagnosed much earlier, and potentially before the onset of loss of language or motor function.

There may also be scope in the future for more widespread enzyme testing of newborns, or use of genetic testing to identify CLN2, but this is not currently in use in the NHS.

#### *2.2.4.2 Treatment*

Treatment and management of CLN2 has typically involved therapy to ease or manage symptoms, such as speech therapies for speech delay and anticonvulsants for managing seizures. This is described in full in CS Section B.1.3.5.3.

Treatment with cerliponase alfa should begin when a diagnosis of CLN2 is confirmed, irrespective of the patients ML scores or other factors. Clinical advice to the EAG was that treatment may not be beneficial to patients with very low ML score (ML score of 1 or 0) as treatment may not improve quality of life.

### 2.2.5 Intended positioning of cerliponase alfa

The company expects that cerliponase alfa will be used in all CLN2 patients irrespective of age or disease progression at time of treatment initiation. The EAG agrees with the company's proposed positioning of cerliponase alfa in patients with CLN2. This is in line with the anticipated marketing authorisation and the respective studies, study 190-201/202, study 190-203 and MAA study populations.

The EAG notes that, given clinical advice, treatment might not be initiated in patients with advanced disease (e.g. ML scores of 0 or 1), because of current uncertainty as to whether treatment will benefit patients with advanced disease.

### 2.2.6 Equality considerations

As noted in section B.1.4 of the CS, the EAG agrees that there are no issues relating to equity or equality when using cerliponase alfa.

## *2.3 Critique of company's definition of decision problem*

The company's population, intervention and comparator were in line with NICE final scope. The EAG presents a summary of the decision problem as defined by NICE, the CS and EAG critiques in Table 2

### 2.3.1 Population

The EAG agree that the population presented in the CS is in line with the final scope issued by NICE. All 35 CLN2 patients in the MAA study, which included one participant that transitioned from Study 190-203, four CLN2 patients from Study 190-201/202, and six CLN2 patients from Study 190-502, were from the UK. . CLN2 is an ultra-rare condition with about 50 people currently diagnosed in the UK. The EAG agrees that the population described in the CS reflected the characteristics of the patient population in England and Wales.

### 2.3.2 Intervention

The intervention in the company's submission (cerliponase alfa) is in line with the NICE scope.

### 2.3.3 Comparator

The current UK practice on the management of CLN2 (i.e. palliative care) treats symptoms relating to CLN2 (such as seizures, dystonia, and speech delay) but not the cause of CLN2. The positioning of cerliponase alfa in the clinical pathway by the company is in line with NICE final scope.

### 2.3.4 Outcomes

The outcomes presented in the CS broadly reflect those listed in the final scope. The company provided rationales where adjustments were made. The primary outcome was the CLN2 clinical rating ML subscale. The EAG notes that the CS did not include substantive data on vision and seizure components of the CLN2 MLVS scale, or on total MLVS score. These were requested by the EAG and subsequently supplied by the company.

The EAG notes some concerns with the limited reporting of outcomes in the CS, particular in relation to quality of life, vision and seizures. The EAG also notes that outcome reporting beyond the MLVS scale, such as need for additional medical care, neurological development and frequency and nature of seizures, was very limited.

### 2.3.5 Subgroups

The CS included some limited subgroup analyses by stage of progression. The EAG considers that subgroup analyses of outcomes would have limited statistical power because of the sample size in each study.

**Table 2 Summary of decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| **Population** | People with CLN2 | Aligned with scope | N/A, no difference from final scope | The population is in line with the final scope and is representative of the UK population. |
| **Intervention** | Cerliponase alfa | Aligned with scope | N/A, no difference from final scope | The intervention, cerliponase alfa, is in line with the final scope. |
| **Comparator(s)** | Established clinical management without cerliponase alfa (including managing the symptoms and complications associated with CLN2) | Aligned with scope | N/A, no difference from final scope | This is in line with the final scope. |
| **Outcomes** | The outcome measures to be considered include:<br>Symptoms of CLN2 including visual function, seizures, myoclonus, dystonia, spasming, pain, and feeding<br>Disease progression<br>CLN2 Clinical Rating Scale (reported as 4-domain scale and combined score of the motor and language domains)<br>Weill Cornell LINCL Scale (4-domain scale)<br>Hamburg scale<br>Neurological development which may be informed by measures specified in the MAA for HST12 including Bayley Scales of Infant Development III, WPPSI-IV, Vineland Adaptive Behaviour Scale, and WISC-V<br>Need for medical care (including hospitalisation, emergency care and primary and secondary care appointments, and concomitant medication)<br>Mortality<br>Adverse effects of treatment (including immune response and effects and complications related to treatment administration) | Aligned with scope (see rationale) | Note that the focus of the majority of analyses is based on disease progression, using the CLN2 Clinical Rating Scale; an adapted version of the Hamburg scale. This submission will focus on the CLN2 Clinical Rating Scale, including a 2-domain (motor and language) subscale called the ML scale.<br><br>Note that whilst 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. Full details on outcomes reported according to the relevant study are covered in Section B2.4<br><br>The only need for medical care variable collected was seizures that require doctor/hospital visits. No other need for medical care | The EAG notes that 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).<br><br>The EAG acknowledges that not all the outcomes were collected in the included studies, and that the company's approach of supplying data from other sources is reasonable.<br>The EAG notes the lack of evidence on neurological development and need for medical care. |

| | | | | |
|---|---|---|---|---|
| | 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 | | information was collected as part of the clinical evidence. No other differences from final scope. | |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. 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. | Aligned with scope where relevant | Cost-effectiveness analysis aligned with reference case. However, 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. | The EAG considers that the 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. |
| **Subgroups** | If the evidence allows, the following subgroup should be considered:<br>Stage of progression of CLN2 | Aligned with scope | Cerliponase alfa is a relevant treatment for all patients covered by the marketing authorisation. However, scenario analyses are presented in which alternative baseline health state distributions are considered. | The CS reported some limited subgroup analyses. The EAG considers that subgroup analyses based on age and ML score at treatment initiation may have been helpful but would have limited statistical power |

# 3 CLINICAL EFFECTIVENESS

## *3.1 Critique of the methods of review*

***Searches***

The original company submission included searches to identify clinical evidence for patients with CLN2 disease. A description of the searches and some of the search strategies were included in Appendix D (pages 6-23). In response to the EAG's points for clarification, a further document was provided by the company, which included explanations for errors identified by the EAG. Table 44 in Appendix 1 presents a critique of the searches.

***Inclusion criteria***

The review inclusion criteria were very broad, including studies of any intervention or comparator and case reports. Screening was undertaken by two reviewers working independently, with disagreements resolved through discussion, or by a third reviewer. Thirty-seven further studies were included in the company's updated review; when added to the 33 publications included in the original 2017 review, this resulted in a total of 70 included studies.

***Critique of data extraction***

Data extraction methods were appropriate, being performed by one reviewer and checked by another No details were reported about how discrepancies were resolved.

***Quality assessment***

Single-arm trials and non-comparative cohort studies were assessed for bias using a modified Critical Appraisal Skills Programme (CASP) checklist. Assessments were performed by one reviewer and checked by another, although no details were provided about how discrepancies were resolved.

***Evidence synthesis***

Included study details and results were tabulated in Appendix D of the submission, but no narrative synthesis covering all the included studies was presented. The EAG therefore examined the table of studies and noted that some of the recent cerliponase alfa studies were large enough and/or had long enough follow up to be useful further sources of evidence for the appraisal, beyond the studies discussed in the company's main submission (i.e. Document B). These mainly related to device-related adverse events and are discussed in Section 3.5.

## *3.2 Studies on the clinical efficacy and safety of cerliponase alfa*

### 3.2.1 Summary of included studies

The company presented an overview of the cerliponase alfa clinical programme in CS section B.2. The company included nine trials or studies in its submission. A summary of these studies and their characteristics are reported in Table 3. Full study characteristics are presented in Table 9, and Table 10 of the CS and in the supplied CSRs.

Studies 190-202 and 190-203 were the primary sources of clinical evidence on cerliponase alfa; 190-202 was an extension of the original 190-201 trial which was considered in the previous appraisal. Both trials were single-arm evaluations of cerliponase alfa. Additional evidence on clinical outcomes was supplied for the managed access agreement (MAA) cohort. Studies 190-501, 190-502, and 190-504 assessed the long-term safety of cerliponase alfa, and study 190-801 assessed other relevant clinical outcomes including dystonia, myocloni, health-related quality of life outcomes and seizures.

There are four ongoing studies investigating cerliponase alfa for CLN2, which are: study 190-801[24] (proposed to end in 2027), study 190-501 [13] (proposed to end in 2030), study 190-504 [25] (proposed to end in 2029) and study 190-506 [26] (proposed to end in 2029). Study 190-801 is a long-term effectiveness study, study 190-501, 190-504 and study 190-506 are long-term safety studies. Interim evidence from 190-501 and 190-504 were used to inform the safety evaluation of cerliponase alfa in the company submission.

**Table 3 Summary characteristic of the studies included in the company submission**

| Study | Registry No. | Study design | Weeks of follow-up | Dose | Sample size | Primary outcome | Mean age* (SD) | Mean ML score* (SD) | % with ML score=6* |
|---|---|---|---|---|---|---|---|---|---|
| 190-201 | NCT01907087 | Single arm interventional | 48 | 300 mg± | 24 (one person not followed up in 190-202) | CLN2 rating scale (Adapted ML subscale) | 5.0 (1.29) | 3.5 (1.18) | 8 |
| 190-202 | NCT02485899 | Long term FU of 109-201 cohort | 240 | | | | | | |
| 109-201/202 | NCT01907087/ NCT02485899 | Long term FU of 201/202 cohort | 280 (this included 24 weeks of safety follow-up) | | | | | | |
| 190-203 | NCT02678689 | Single arm interventional | 169 | 300mg for aged ≥ 2 years 100-200mg for up to 2 years, dependent on age | 14 | CLN2 rating scale (Adapted ML subscale) | 3.1 (1.45) | 4.64 (1.69) | 50.0 |
| MAA cohort | NA | Clinical data collection agreement | 209 | 300 mg± | 35 26β | CLN2 rating scale (Adapted ML subscale) | 4.37 (1.07) β | 4 (1.26) β | 11.54 β |
| 190-501 | NA | Post-marketing, observational safety study | 104 | 300 mg± | 37 31β | Long term safety | 7.1 (3.4) | 3.8 (1.23) β | NR |
| 190-502 | NCT02963350 | Open label, expanded access program/ compassionate use | 31 | 300 mg± | 27 11β | Safety and tolerability, and Expand access | 5.7 (3.28) | 3.6 (1.43) β | NR |
| 190-504 | NA | Observational, post-authorisation safety study | 151 | 300 mg± | 48 | Long term safety | 7.4 (3.0) | 4.0 (1.33) | NR |
| DEM-CHILD-RX | NA | Registry study | 26† | 300mg for aged ≥ 2 years 100-200mg for up to 2 years, dependent on age | 21 | CLN2 rating scale (Hamburg ML subscale) | 4.7 (1.94) | 3.9 (1.6) | 24 |
| 190-801 | NA | DEM-CHILD registry study | NA† | 300 mg± | 24 | Clinical outcomes (seizures and movement disorder like myoclonus, dystonia) | 5.1 (2.3) | 3.92 (1.59) | 25 |
| 190-901 | NA | NH control study | NA | NA | 74 42β | CLN2 rating scale (Hamburg ML subscale) | 4.0 (0.92) β | 4.48 (0.77) β | 0β |

* At baseline, †Participant follow-up was started at different timepoints, duration of follow-up therefore varied for patients (minimum follow-up was 6 months); ± all participants were aged ⩾2 years; β values reported based on reduced sample size like MAA cohort in document B, study 190-501 in CSR, study 190-502 in CSR, and study 190-901 in CSR (evaluable population). Study 190-901 analysis included some DEM-CHILD patients, and the mean age is based on age at diagnosis not age at baseline; NA is Not applicable, NR is Not reported; CLN2 Neuronal ceroid lipofuscinosis type 2, FU Follow up, NH natural history.

#### *3.2.1.1 Summary of population characteristics and outcomes evaluated*

Table 3 summarises key characteristics of the studies included in the submission. Of the two main efficacy trials, study 201/202 had both the largest sample size (n=24) and the longest follow up (239 weeks).

In terms of mean age and the proportion of patients with ML scores of 6, study 201/202 is more aligned with the NHS MAA cohort, than study 190-203 is; half the patients in study 190-203 had a baseline ML score of 6 compared with around 12% in the MAA cohort. The EAG therefore notes that study 190-203 may not be representative of patients likely to treated with cerliponase alfa at the present time, as patients in the study were mostly younger and with less advanced disease. However, it may represent a population that might be treated with improved, earlier, diagnosis.

The number of patients presenting with atypical CLN2 was not collected in studies 190-201/202, 190-203 or the MAA.

The primary outcome in all the efficacy studies was the combined motor and language domains of the CLN2 clinical rating scale, which was developed for use in these studies. The company's focus on this outcome in its trials and submission presented a less comprehensive evaluation of patient outcomes than when using the full CLN2 rating scale scores which cover all four domains: motor, language, vision and seizures (MLVS). The EAG therefore requested MLVS results for all studies at the clarification stage.

#### *3.2.1.2 Natural history cohort (study 190-901)*

The EAG notes that study 190-901 was conducted some years before the studies of cerliponase alfa. Therefore, there may have been changes in the standard of care which may have improved outcome and quality of life. Clinical advice to the EAG suggested though that standard care has not changed substantially in recent years, so overall survival and rate of progression of CLN2 without cerliponase alfa has not substantially altered. Hence, the EAG considers that study 190-901 is still an appropriate comparator study for this assessment.

#### *3.2.1.3 Matching between cerliponase alfa and natural history cohorts*

Patients from study 190-901 were matched with patients in the cerliponase alfa studies to compare cerliponase alfa to standard care. There were 42 evaluable patients in study 190-901. The company reported that patients in study 190-901 were matched on the ratio of 1:1 with patients in study 190-201/202, the MAA cohort and DEM-CHILDRX to ensure a unique pair of patients between the two arms. However, a 3:1 matching was used for the comparison with 190-203, using weighted inverse approach. In the analysis pooling all studies, requested by the EAG at time of clarification, a 1:1 matching was used.

Patients were matched by CLN2 ML score at baseline and by age (within 3 months). In 190-201/202 and 190-203 patients were also matched by genome with equal number of common alleles. Table 4 summarises the patient characteristics after matching. The EAG notes that there is good balance between the cerliponase alfa and natural history groups for the matching criteria. However, as only three criteria were used for matching there could be important patient characteristics that have not been properly matched for. In clarification question A6, the EAG asked to company to provide details about how these variables were identified but few details were provided about why these particular variables were used.

The EAG notes that the simple matching approach used could lead to bias because some patients were excluded from the matching, and it is unclear to the EAG whether these patients had comparable characteristics and outcomes to included patients. Ideally a more sophisticated approach to matching should have been used, such as propensity weighting or matched adjusted indirect comparison.

**Table 4: Summary characteristic of the matched two arm studies included in the company submission.**

| MSA | Studies in CS | Sample size | Weeks of follow-up | Mean age* (SD) | Mean ML score* (SD) | % with ML score=6* (n) | Sex % female |
|---|---|---|---|---|---|---|---|
| 1 | 109-201/202 | 17 | 239 | 4.6 (0.74) | 3.40 (1.33) | 12 (2) | 65 |
| | 190-901 | 17 | | 4.6 (0.72) | 3.40 (1.33) | 12 (2) | 41 |
| 2 | 190-203 | 12 | 169 | 2.7 (1.12) | 5.0 (1.41) | 58 (7) | 66.7 |
| | 190-901 | 29 | | 2.7 (1.09) | 5.0 (1.38) | 62 (18) | 52.8 |
| 3 | MAA cohort FAS | 26 | 209 | 4.37 (1.07) | 4 (1.26) | 11.54 (3) | 23¶ |
| | 190-901 | 26 | | 4.35 (1.11) | 4 (1.26) | 11.54 (3) | 50 |
| 4 | MAA Cohort new starter | 17 | 209 | 4.56(1.10) | 4.12 (1.11) | 11.8 (2) | NA¶ |
| | 190-901 | 17 | | 4.53 (1.18) | 4.12 (1.11) | 11.8 (2) | 53 |
| 5 | DEM-CHILD-RX | 21 | 26† | 4.7 (1.94) | 3.90 (1.58) | 24 (5) | 52 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | DEM-CHILD-NH | 21 | | 4.7 (1.92) | 3.90 (1.58) | 24 (5) | 24 |

* At baseline, †Participant follow-up was started at different timepoints, duration of follow-up therefore varied for patients (minimum follow-up was 6 months); ¶Sex not collected as part of MAA, therefore sex % female of participants in MAA new starter cohort is 100% unknown MSA is matched study group; FAS is full analysis set.

### 3.2.2 Summary of statistical analyses

The primary outcome measured by the company was a responder analysis on the 6-point adapted CLN2 ML scale which included two assessments: rate of decline and time to unreversed two-point decline or score of zero in CLN2 scores by week 48. The time from baseline to first unreversed two-point decline or total score of zero were summarised using the Kaplan Meier estimates and Cox proportional hazards model.

The rate of decline scaled to a 48-week time-period was calculated for each individual patient in the study using slope analysis, as explained in section B.2.4.1.4 of the CS. The EAG notes that this analysis does not account for the categorical nature of the CLN2 scales, that progression over time is probably not smooth or linear in nature, and that it does not take into consideration baseline variables like age, ML score and sex.

Secondary outcomes measured by the company included, overall survival, change from baseline on MRI measures, and various exploratory endpoints (OCT, VA, EEG, Denver II developmental screening test, PedsQL, CLN2 disease based QoL, and EQ-5D-5L questionnaire).

The number of patients experiencing seizures and the frequency of the seizures were reported descriptively using percentages and graphs. The severity and number of patients experiencing movement disorder (dystonia and myocloni) was reported descriptively.

## *3.3 Primary outcome: CLN2 rating scale*

In the CS all clinical effectiveness results were presented separately for each trial. Given the similarity in conditions, patient populations and results across the included trials and the managed access cohort, the EAG requested that all data sources be pooled together, and statistical analyses be supplied for the pooled data. The company supplied these pooled analyses, and they are reported here as the EAG considers that pooling the results makes for a clearer presentation of the evidence.

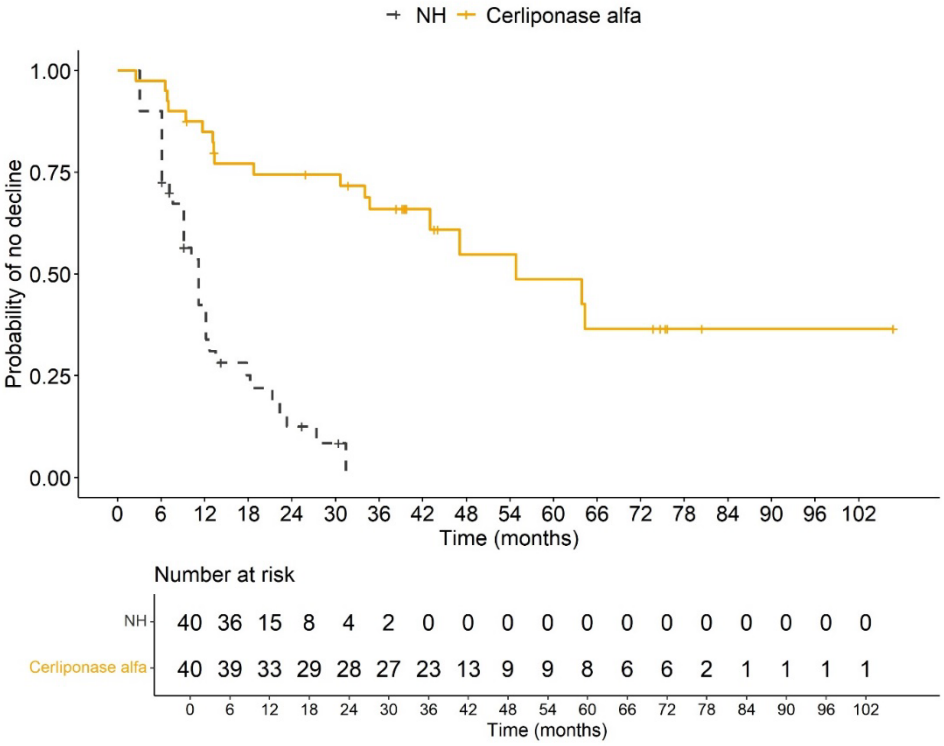
The CS focussed mainly on reporting the motor and language (ML) components of the CLN2 scale. The EAG requested that similar analyses be presented for the full 12-point scale on all four components (MLVS, motor, language, vision and seizures) and for each sub-scale separately. These were supplied by the company.

In all analyses supplied by the company, results from trials of cerliponase alfa were compared to matched patients from the natural history cohort (190-901). Although, strictly, these are indirect comparisons, they are included in this section for convenience.

### 3.3.1 ML Scale

Figure 2 shows the Kaplan-Meier curve for experiencing an unreversed 2-point decline in ML score (or reaching a score of zero) in all cerliponase alfa patients (190-202, 190-203 and MAA) compared to matched natural history patients (190-901). Nearly all natural history patients had declined within two years, whereas only about 25% of patients on cerliponase alfa had a 2-point decline within two years. Median time to a 2-point decline with cerliponase alfa was around four and a half years. The hazard ratio comparing cerliponase alfa to natural history was 0.139 (95% CI 0.068 to 0.287). There is therefore strong evidence that cerliponase alfa slows the decline in motor and language function.

**Figure 2 : Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-ML score or score of zero [Clarification response Figure 3]**




When examining time to an ML score of zero, all natural history patients had declined to a score of zero within about three years. By contrast, only three cerliponase alfa patients declined to a score of zero at all (Hazard ratio 0.005; 95% CI 0.001 to 0.040)

In the regression analysis of decline in ML score over time patients on cerliponase alfa had a typical decline of 0.32 points per 48 weeks (so around 1 point every 3 years). Natural history patients had a rate of decline of 1.26 points every 48 weeks. The EAG notes that this rate of decline is unlikely to be

constant across patients, as patients appear to experience varying rates of decline. It is also unlikely that any decline in function will be smooth over time, as patients often had long periods of stable scores and then sudden fluctuations or declines in scores.

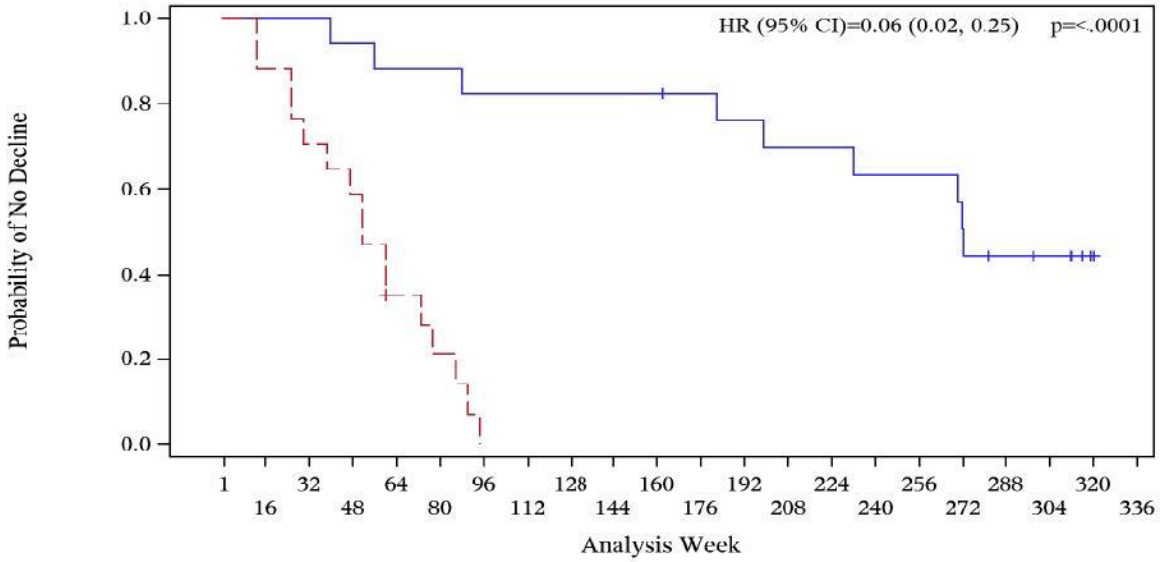
The rate of decline with cerliponase alfa also varied across the three main sources of evidence: it was 0.42 points per 48 weeks in 190-202; 0.15 points per 48 weeks in 190-203; 0.23 points per 48 weeks in the managed access patients (see Table 5). These variations may be at least in part due to shorter follow-up in 190-203 and MAA. In the longer follow-up period in trial 192-202 around 6 of the 23 patients experienced declines of 1 or 2 points in ML score in the fourth or subsequent year of follow-up (from CSR for Trial 190-202). The EAG notes that it was unable to reproduce the numbers in Table 5 in our own analysis, see Section 3.8 for a discussion of this issue.

**Table 5 Rates of decline in ML score and hazard ratios by study**

| **Study** | **Decline in ML score (points per 48 weeks)** | **Hazard ration for unreversed 2-point decline in ML score** |
|---|---|---|
| 190-202 | 0.42 (95% CI: 0.12 to 0.71) | 0.060 (95% CI: 0.02 to 0.25) |
| 190-203 | 0.15 (95% CI: 0 to 0.30) | 0.091 (95% CI: 0.021 to 0.393) |
| MAA | 0.23 (95% CI: -0.03 to 0.50) | 0.126 (95% CI: 0.05 to 0.31) |

The Kaplan-Meir curve for experiencing an unreversed 2-point decline in ML score in trial 190-202 is shown in Figure 3 (after CS Figure 4). While there is still a very substantial difference between cerliponase alfa and natural history patients (HR 0.06, 95% CI 0.02 to 0.25), the curve suggests that many cerliponase alfa patients are experiencing a two-point decline only after around 176 weeks (around 3.5 years). The 190-202 trial also had a faster rate of decline in ML score of 0.42 points per 48 weeks (or 1 point every 2.5 years). This may be a consequence of longer-term follow-up beyond 3 years in that trial.

**Figure 3 Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-ML score or score of zero in 190-202 (CS Figure 4)**



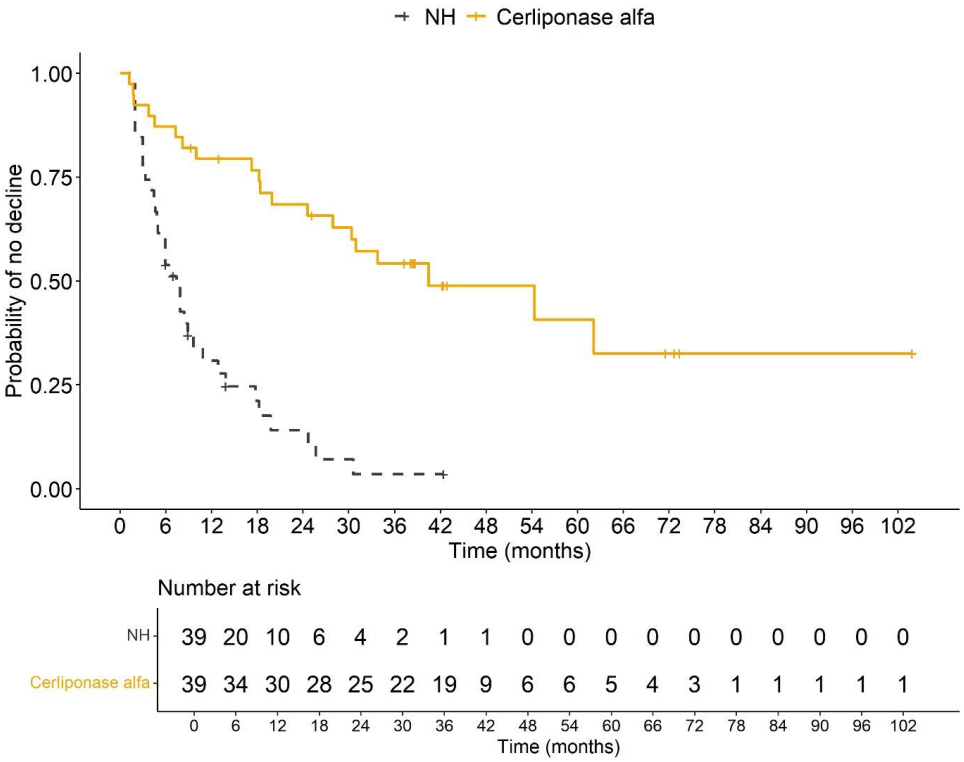

There may also be variation in the efficacy of cerliponase alfa depending on ML score at initiation of treatment. Of the patients with an ML score of 6 at treatment initiation (i.e. no deterioration in motor function or language) most had no decline at all during follow-up. However, the only two such patients with a follow-up of over three years in trial 190-202 did experience a rapid two- or three-point decline in ML score after four years of follow-up. Hence starting treatment at an ML score of 6 might lead to a longer period of stability, or a slower rate of decline. This is not conclusive, due to the small number of patients with an initial ML score of 6.

The EAG notes that patients with an initial ML score of 6 tend to be younger as their condition was detected earlier, before onset of language or motor symptoms. Hence any possible greater benefit in patients who initiate treatment at ML 6 may be confounded with any benefit of initiating treatment at a younger age.

### 3.3.2 MLVS scale

Figure 4 shows the Kaplan-Meier curve for experiencing an unreversed 2-point decline in the full MLVS score (or reaching a score of zero) in all cerliponase alfa patients (190-202, 190-203 and MAA) compared to matched natural history patients (190-901). Median time to a 2-point decline with cerliponase alfa was around three years. The hazard ratio comparing cerliponase alfa to natural history was 0.17 (95% CI 0.089 to 0.322). There is therefore strong evidence that cerliponase alfa slows the decline in MLVS score as a whole. The slightly higher rate in decline in MLVS score when compared to ML (motor and language) alone is probably due to decline in vision (see Section 3.3.3)

**Figure 4 Kaplan-Meier curve for time to unreversed 2-point decline in CLN2-MLVS score or score of zero [Clarification response Figure 10]**




When examining time to an MLVS score of zero, the Kaplan-Meier analysis suggested that more than half of the natural history patients will decline to a score of zero within about four years. By contrast, only one cerliponase alfa patient declined to a score of zero at all.

In the regression analysis of decline in MLVS score over time patients on cerliponase alfa had a typical decline of 0.39 points per 48 weeks (so around 1 point every 2.5 years). Natural history patients had a rate of decline of 2.12 points every 48 weeks.

Based on limited patient-level data presented in CSRs there is evidence that actual trends over time in MLVS may be very variable across patients. Some patients had increases in score over time, or highly fluctuating scores. This may be because of fluctuations in seizure score (see Section 3.3.3). Patients with a high initial MLVS score of 10 or more typically had no substantial reduction in MLVS score, during follow-up. However, most of these patients were in trial 190-203 with a follow-up of three years.

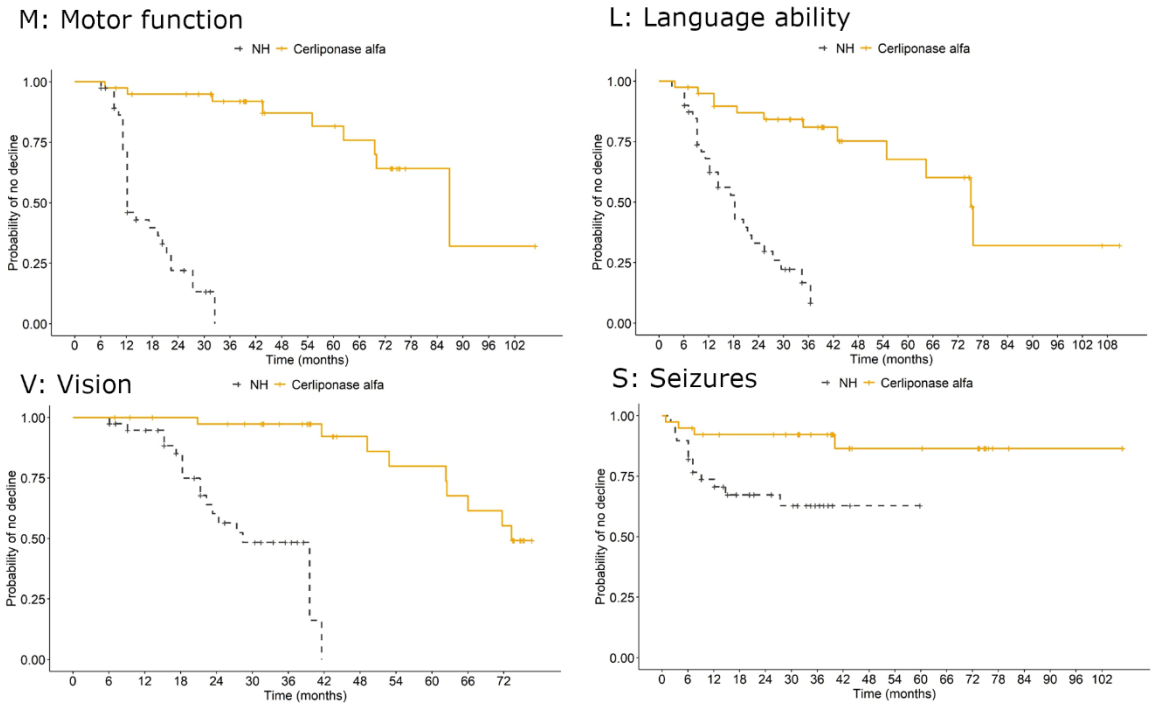
### 3.3.3 CLN2 subscales

Figure 5 shows the Kaplan-Meier curve for experiencing an unreversed 2-point decline in each of the four CLN2 subscales (Motor, Language, Vision, Seizures) in all cerliponase alfa patients (190-202, 190-203 and MAA) compared to matched natural history patients (190-901).

For the motor and language subscales all natural history patients Kaplan-Meier curves suggested all patients are likely to decline by at least two points within three years. Decline in vision was slower, but patients are predicted to lose at least two points in vision score within 3.5 years. About 40% of natural history patients lost 2 or more points on the seizure scale within three years.

Cerliponase alfa slowed progression on all four subscales. For motor function only around 25% of patients are predicted to experience a two-point decline within 5-6 years, based on Kaplan-Meier curves. Language appears to be lost faster, with around half of patients likely to lose two-points within 5-6 years. There is some evidence that vision is preserved for a time, with little vision loss in the first three years of treatment, but vison appears to be lost rapidly thereafter. Very few patients on cerliponase alfa experienced a two-point loss on the seizure subscale.

**Figure 5 Kaplan-Meier curve for time to unreversed 2-point decline in each of the 4 CLN2 subscale scores (or score of zero) [from response to clarification]**




Hazard ratios for all subscales are summarised in Table 6. Cerliponase alfa substantially reduced the hazard of decline in all four subscales when compared to matched natural history patients.

**Table 6 Hazard ratios when comparing cerliponase alfa to natural history for the four CLN2 subscales**

| Subscale | Hazard ratio | 95% CI |
|---|---|---|

| | | |
|---|---|---|
| Motor | 0.023 | 0.006 to 0.089 |
| Language | 0.114 | 0.048 to 0.271 |
| Vision | 0.013 | 0.002 to 0.072 |
| Seizures | 0.214 | 0.066 to 0.695 |

The average rate of decline (in points per 48 weeks) is shown in Table 7 for all four subscales. For natural history patients, rates of decline in motor, language and vision are around one point every two years. With cerliponase alfa rates of decline are slower, at around one point every 5 or 6 years for motor function and language. The rate of decline in vison was also slowed, but, as seen in , there may be faster loss of vison at later follow-up times. The EAG notes that this might be influenced by trial 190-203, which had many younger participants with no decline in vision (i.e. continued at a score of 3) throughout the trial. There was no clear evidence of any decline over time in the seizure score, but this appears to fluctuate substantially over time.

**Table 7 Rate of decline for the four CLN2 subscales**

| **Subscale** | **Mean rate of decline (points per 48 weeks, with SD)** | |
|---|---|---|
| | Natural history | Cerliponase alfa |
| Motor | 0.69 (0.48) | 0.19 (0.56) |
| Language | 0.58 (0.49) | 0.13 (0.17) |
| Vision | 0.55 (0.46) | 0.23 (0.28) |
| Seizures | 0.20 (0.62) | -0.17 (0.49) |

## *3.4 Other outcomes*

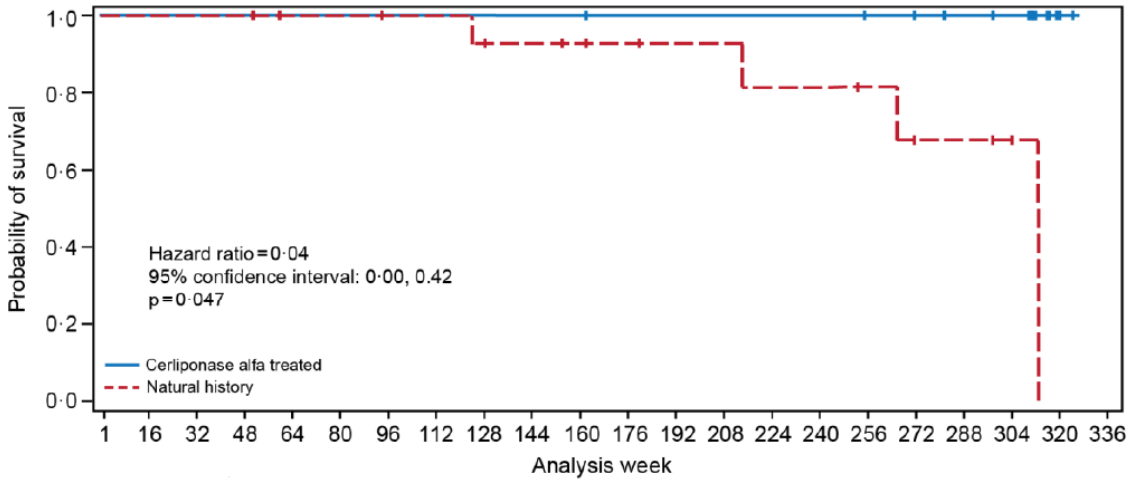
### 3.4.1 Overall survival

No deaths on patients with cerliponase alfa were reported in studies 190-201/202, 190-203, and 190-502. One death was reported in Study 190-504, which was assessed as unrelated to the drug or the ICV. One death was recorded in a nine-year-old participant, in study 190-501, after termination of cerliponase alfa treatment. [redacted].

Given the small number of deaths to date with cerliponase alfa the EAG considers that a formal analysis of survival is not feasible. Figure 6 shows the Kaplan-Meier survival curve for the natural

history patients (from CS Figure 9). This suggests that, without treatment, around 30 to 40% of patients will have died within 6 years of diagnosis.

**Figure 6 Kaplan-Meier curve of overall survival in natural history patients (CS Figure 9)**




### 3.4.2 Other vision data

The evaluation of the effect of cerliponase alfa on vision was presented in section O.4 in Appendix O of the company's submission. Visual acuity (VA) and optical coherence tomography (OCT) were measured in study 190-201/202 and study 190-203. In addition, an electroretinogram was carried out in the MAA cohort study. Generally, the company considered that there was no evidence that cerliponase alfa improves or stabilises vision loss.

Additional data was supplied at time of clarification. In study 190-202 bilateral atrophy was the most reported form of visual deterioration (in 9 patients). Two patients had reductions in retinal thickness and two had retinopathy. In study 190-203 nine of twelve patients had an abnormal OCT at their final assessment: no further details were provided.

The EAG agrees that the results presented by the company do not provide any evidence that cerliponase alfa improves or stabilizes vision loss in the longer term.

### 3.4.3 Other seizure data

The company presented additional seizure data collected from a supplementary study, 190-801, and study 190-203.

In study 190-203, the modified unified Batten Disease rating scale (mUBDRS) seizure inventory was used to gather more information on seizure for patients treated with cerliponase alfa. Out of the 14 CLN2 patients in 190-203, 5 patients improved between 1 and 6 points, 3 patients lost between 1 and 5 points, and 6 patients had no change in their scores from baseline.

In study 190-801 wave 1 analysis (Appendix Q of CS and the 190-801 CSR) the company measured the percentage of CLN2 patients treated with cerliponase alfa that experienced seizure, alongside the type of seizures, and the frequency of the seizures.

The results from the CLN2 disease seizure inventory showed that the primary generalised seizures, atonic seizures, and tonic-clonic seizures were the most common seizures experienced by the patients compared to the complex partial seizures, simple partial seizures, and myoclonic seizures. In addition, the percentage of patients experiencing seizures over the duration of the study were fluctuating and the number of patients being evaluated were declining (page 14 of 25, of 190-801 wave 1 CSR). There was an increasing percentage of patients experiencing seizures within the first year of treatment, then, there was a decline over some period (approximately 20 months) and a rise towards the fourth year of being on treatment.

The percentage of patient caregivers reporting seizures was over 50% throughout the study period. However, the number of patient caregivers reporting that patient safety was a problem because of seizure activity was low.

Generally, the company suggest that the frequency of seizure in CLN2 patients treated with cerliponase alfa is stable over the observational study and the severity of seizures is low as the proportion of participants that required a doctor or hospital visit was very low across the observation period.

Clinical advice to the EAG suggested that cerliponase alfa reduces the severity of seizures and reduces the frequency of seizures in CLN2 patients treated with cerliponase alfa.

Electroencephalogram (EEG) was measured in 190-201/202, study 190-203 and MAA cohort study. It was used to assess the epileptiform activity and / or frequency slowing, in combination with the activity's location (focal vs generalised) at baseline and at any time after initiation of treatment in CLN2 patients. One patient in study 190-203 experience a non-serious AE of abnormal EEG, however it was assessed as a grade 1 and not related to the treatment. The results from study 190-201/202, study 190-203, and MAA cohort study showed that there was no relevant clinical changes or new safety concerns.

Clinical advice to the EAG suggested that there is no EEG safety concerns for CLN2 patients treated with cerliponase alfa.

### 3.4.4 Brain atrophy (assessed using MRI)

Brain atrophy assessments were listed as a key secondary outcome in the efficacy studies although they were not performed in the natural history patients, so comparisons between groups were not possible. At week 145, the mean change from baseline in grey matter volume was –13% in study

201/202 and –10% in study 203. For the MAA cohort, the CS stated that due to the nature of reports and a lack of consistency in assessing MRI results, no conclusions could be made.

### 3.4.5 Neurological development outcomes

Annual collection of data for the following outcomes was specified in the MAA: Bayley Scales of Infant Development III (BSID-III), Wechsler Pre-School and Primary Scale of Intelligence (WPPSI-IV), and Vineland Adaptive Behaviour Scale (VABS). However, no summary data for these outcomes were presented in the submission, which noted that patients were often unable to complete many of the assessments due to problems with neurodevelopment, age, and vision.

### 3.4.6 Myoclonus and dystonia

Limited data on myoclonus and dystonia were available, predominately from trial 190-801. Myoclonus and feeding (or swallowing) scores were also collected every six months in the MAA cohort. No data on natural history patients were available.

One-third of patients in trial 190-801 had onset of myocloni within 60 months, with a median time to fist myocloni of 71.4 months. 25% of patients had sustained worsening in frequency of myocloni with a median onset time of 68.9 months. All patients had onset of dystonia within 36 months, with a median onset time of 19.4 months. All patients had sustained worsening in frequency of dystonia with a median onset time of 27.6 months. In the MAA new patient cohort mean myoclonus scores declined initially over the first 30 months (from about 2.6 to 1.5) before stabilizing between the ranges of 1.5 and 2.

The mean feeding scores for new patients in the MAA cohort study were stable (between 2.5 and 3) over the duration of the study.

### 3.4.7 Quality of life

Table 8 summarises the HRQoL outcomes recorded in studies and the data actually reported in the company's submission. The submission stated that it was not possible to produce comparative results; no longitudinal studies measuring HRQoL in untreated CLN2 patients were identified in the company's systematic review (Appendix D). In light of this, it is difficult to meaningfully compare results across studies. Difficulty in interpreting the HRQoL data is exacerbated by the company's reporting: the EAG notes that no HRQoL results were reported for studies 190-203 and 190-801, despite several outcomes being evaluated in both studies. Also, both studies 190-201/202 and 190-203 had protocol amendments in which EQ-5D-5L assessments were removed "*in order to decrease study burden and the determination that the other Quality of Life questionnaires administered may be more relevant to this patient population*". Although some EQ-5D-5L data were collected in study 201/202, none were reported.

The EAG also notes further difficulties in interpreting the quality of life data since the questionnaires were completed by parents who were aware that their child was taking cerliponase alfa (i.e. they were not blinded) and who might be aware that their questionnaire responses could have an impact on clinician decisions to discontinue treatment (particularly so in the MAA cohort), especially where ML scores are low (i.e. 2 or lower). Although these methodological issues are unavoidable, they may explain why the HRQoL results may not correlate well with the ML data. For example, the CLN2 QoL results for study 190-202 (see p174 of the CSR) show that, at week 240, there was no change in mean scores from baseline. This is surprising given that by that timepoint 6 of 17 patients had had an unreversed 2-point decline or score of 0 in ML score (see Figure 4 of the CS). Similar lack of correlations were seen in study 190-202 for PedsQL and in the MAA cohort results (compare Figure 15 of the CS with results in the table below). The importance of this issue could be contextualised by evaluating HRQoL and ML score data for natural history patients, though no such dataset has been identified. The EAG concludes that the reliability and clinical validity of the HRQoL data is highly uncertain.

**Table 8 Evaluation and reporting of HRQoL outcomes in the cerliponase alfa studies**

| Study | Outcomes evaluated | Outcome data reported |
|---|---|---|
| 190-201/202 | EQ-5D-5L, PedsQL, CLN2 QoL | EQ-5D-5L: No summary data were reported in the company's submission<br>PedsQL Parent Report for Toddlers: mean change from baseline to month 18 was -4.3 (n=23) and to month 60 was –15.0 (n=18)<br>Peds QL Family Impact Module: mean change from baseline to month 18 was 3.7 (n=23) and to month 60 was –2.4 (n=20)<br>CLN2 QoL: In 190-202, mean change from baseline to month 18 was 5.2 (n=22) and to month 60 was –0.6 (n=19) |
| 190-203 | EQ-5D-5L, PedsQL, CLN2 QoL, ITQoL | No summary data were reported in the company's submission, nor in the CSR. |
| MAA cohort | EQ-5D-5L, PedsQL, CLN2 QoL | EQ-5D-5L: mean change from baseline –0.03 at 18 months (n=14), and change from baseline of 0.024 at 42 months (n=6)<br>PedsQL, New cohort: mean change from baseline of –2.22 at 18 months (n=14), and of 0.14 at 42 months (n=6)<br>CLN2 QoL: mean change from baseline of 1.69 at 18 months (n=14), and of –2.87 at 42 months (n=6) |
| 190-801 | EQ-5D-5L, PedsQL, ITQoL97 | No summary data were reported in the company's submission, nor in the Wave 1 interim summary document |
| DEM-CHILD-RX | EQ-5D-5L, PedsQL, CLN2 QoL, ITQoL | EQ-5D: Mean VAS change from baseline was [redacted] at 48 months (n=4)<br>PedsQL Parent Report for Toddlers: Mean (SD) total change from baseline was [redacted] at 18 months [redacted] after 30 months (n=4) |

| | | |
|---|---|---|
| | | PedsQL Family Impact Module: Mean (SD) total score change from baseline was [redacted] at 18 months and [redacted] at 48 months (n=4)<br>CLN2-QoL: Total score change from baseline was [redacted] at 18 months and [redacted] at 48 months (n=4)<br>ITQoL97: Parental impact time: Mean (SD) score change at 48 months was [redacted]<br>Overall health score: change from baseline mean (SD) [redacted] after 48 months |

## *3.5 Adverse events and safety data*

The safety of cerliponase alfa was evaluated in Studies 190-201/202, 190-203, 190-501, 190-502, and 190-504. Adverse event reporting was not required as part of the MAA, although ECG assessments were carried out (reported in Appendix R of the CS). Two studies are still ongoing: 190-501 and 190-504 are both long-term (10 years) safety studies, which still have many years to run. Study 190-501 is being conducted only in the United States, study 190-502 in the United States, Germany, Italy and the UK and study 190-504 in Denmark, France, the Netherlands, Sweden, Italy, Germany, Romania, and the UK. Detailed results of all studies were reported in Appendix F of the CS. The most common treatment-related adverse events were pyrexia, hypersensitivity, and vomiting, with most assessed as grade 1 or 2 in severity. A summary of key safety outcomes is reported in Table 34 of the CS, which has been adapted and presented here as Table 10. The number of treatment-related SAEs varied widely across studies. Studies 190-203 and 190-504 report data for similar follow up durations, with the former reporting that 50% of patients had a treatment-related SAE and the latter reporting that only 2% had a treatment-related SAE. Only one patient had an SAE leading to study drug discontinuation, although SAEs leading to dose interruption were more frequent.

### 3.5.1 Device related events – infections and replacements

The incidence of device-related adverse events varied across studies, ranging from 83% in study 201/202 to 11% in study 502 (although the latter study only had 31 weeks of follow up). In study 190-201/202, 15 device-related infections were seen in nine participants. In study 190-203, three patients had device-related infections, though there were no device malfunctions or events leading to the removal and return of an ICV device. In study 190-501, so far 22 device-related infections have been reported in eight participants and five ICV devices were replaced due to AEs in four participants. To date, six events of device-related infection have been reported in two participants in study 190-504. One device-related infection was reported in study 190-502 (this study had a short follow up period).

The company stated in its submission that it has taken steps to reduce the risk of these infections by developing educational materials for healthcare professionals, describing the correct infusion

preparation, the ICV drug administration and patient monitoring. The company's advisers thought that the rate of ICV infusions that lead to infection would be significantly lower in clinical practice. Given that device-related infections were reported in the trials as numbers of events and not as rates, the EAG sought further evidence on this issue.

The EAG asked their clinical adviser what the rate of infections and device replacements were at his centre (Royal Manchester Children's Hospital); infections were extremely rare, there were no problems with any of the device operations and only one patient needed a ICV replacement before four years.

The EAG also notes results from two studies on device-related adverse events which were reported in the company's systematic review (Appendix D) document. A conference abstract by Schwering et al 2021 reported data from more than 3000 intracerebroventricular enzyme replacement therapies in 48 German patients over 6 years for occurrence of device-related adverse events and infections.[27] They found rates for device-related adverse events were 0.27% and device-related infections were 0.33%. This infection rate is higher than the 0.125% the company used in its modelling, which was based on clinical opinion (see Table 75 of the clarification questions response document).

Craven et al 2022, in a study at Great Ormond Street hospital, audited the longevity and survival of the ventricular access devices needed to administer cerliponase alfa via an intracerebroventricular (ICV) route, from January 2014 to June 2020.[28] Twenty-six device operations were performed on 17 patients: 17 primary insertions and 9 revisions. Twelve device operations had an associated complication, including six cerebrospinal fluid infections. Three of 17 patients (18%) needed replacement ICV access device reservoirs well before the 4-year ICV device replacement timepoint stated in cerliponase alfa's SmPC (replacement before 4 years is needed due to material degradation); two of those patients needed three replacement devices within quite short timeframes.

### 3.5.2 ECG abnormalities

Table 9 describes ECG abnormalities over time observed in the MAA cohort, which are reported in full in Appendix R of the CS; two-thirds of patients had an ECG abnormality at the 42 month timepoint.

For the clinical trials, in study 190-202, 22 of the 24 patients had baseline ECGs, of which four were abnormal (but not clinically significant). In study 203, 6 of the 14 patients (43%) had an ECG abnormality at baseline (none were deemed clinically significant). During the trials ECG abnormalities were more frequent in study 190-201/202 than in study 190-203. Seven patients (29%) experienced 15 cardiovascular and ECG AEs in the study 190-201/202 cohort, all of which were

grade 1 or 2 events. In study 190-203, three participants experienced 4 cardiovascular AEs, which included one ECG abnormality.

**Table 9 ECG 12-lead abnormalities reported in MAA participants (adapted from Table 3, Appendix R of the CS)**

| MAA cohort subgroup | Timepoint (months) | ECG-12 abnormality | | Clinically significant ECG-12 abnormality | |
|---|---|---|---|---|---|
| | | N | Yes | N | Yes |
| Ex-trial participants | Baseline | 11 | 1 | 11 | 0 |
| | 12 | 11 | 6 | 11 | 1 |
| | 24 | 11 | 6 | 11 | 1 |
| | 36 | 10 | 7 | 10 | 2 |
| | 42 | 9 | 6 | 9 | 3 |
| New patients | Baseline | 24 | 4 | 24 | 1 |
| | 12 | 15 | 6 | 15 | 1 |
| | 24 | 13 | 7 | 13 | 1 |
| | 36 | 6 | 4 | 6 | 1 |
| | 42 | 6 | 4 | 6 | 1 |

**Table 10 Summary of key adverse event data from the company's submission (adapted from Table 34 of the CS)**

| Type of adverse event | Study | | | | |
|---|---|---|---|---|---|
| | 190-201/202 | 190-203 | 190-501 | 190-502 | 190-504 |
| | Completed in 2020 289 weeks FU | Completed in 2022 169 weeks FU | Ongoing, long term: 104 weeks of 10 years^ | Completed in 2017 31 weeks FU | Ongoing, long term: 151 weeks of 10 years^ |
| | N=24, n (%) | N=14, n (%) | N=37, n (%) | N=27, n (%) | N=48, n (%) |
| Any SAE | 21 (88) | 12 (86) | 17 (46) | 15 (56) | 16 (33) |
| SAEs leading to dose reduction | 12 (50) | 0 | 0 | 0 | 0 |
| SAEs leading to dose interruption | NR | 2 (14) | 4 (11) | 0 | 7 (15) |
| SAEs leading to study drug discontinuation | 0 | 0 | 0 | 0 | 1 (2) |
| Any Grade ≥3 AE | 21 (88) | 10 (71) | 14 (38) | 8 (30) | 12 (25) |
| Any treatment-related AE | 23 (96) | 11 (79) | 11 (30) | 16 (59) | 6 (13) |
| Treatment-related SAEs | 8 (33) | 7 (50) | 2 (5) | 6 (22) | 1 (2) |
| **Adverse events of special interest** | | | | | |
| Status epilepticus | 2 (8) | 1 (7) | 1 (3) | 4 (15) | 2 (4) |
| Hydrocephalus | 0 | 0 | 0 | 0 | 0 |

| Type of adverse event | Study | | | | |
|---|---|---|---|---|---|
| | 190-201/202 | 190-203 | 190-501 | 190-502 | 190-504 |
| | Completed in 2020 289 weeks FU | Completed in 2022 169 weeks FU | Ongoing, long term: 104 weeks of 10 years^ | Completed in 2017 31 weeks FU | Ongoing, long term: 151 weeks of 10 years^ |
| | N=24, n (%) | N=14, n (%) | N=37, n (%) | N=27, n (%) | N=48, n (%) |
| Meningitis | 0 | 0 | 1 (3) | 0 | 3 (6) |
| Hypersensitivity | 18 (75) | 10 (71) | 0 | 7 (26) | 4 (8) |
| Temporally-related events (TREs)* | 24 (100) | 14 (100) | 15 (41) | 19 (70) | 14 (29) |
| Device-related events | 20 (83) | 5 (38) | 19 (51) | 3 (11) | 10 (21) |
| Cardiovascular events | 7 (29) | 3 (21) | 0 | 3 (11) | 0 |
| Unexpected rapid decline in CLN2 score | 0 | 0 | NR | 2 (7) | NR |

FU follow up, N sample size, n number of events, SAE serious adverse event; *TREs defined as events with onset after initiation of study drug infusion and within 24 hours of the start or restart of the infusion, ^Median cerliponase alfa exposure time

### *3.6 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

The CS reported indirect comparisons of cerliponase alfa patients with natural history patients from trial 190-901 using patient-to-patient matching. As the only specified comparator for cerliponase is established clinical management without cerliponase alfa the EAG considers that it is reasonable not to include any other indirect evidence.

### *3.7 Critique of the indirect comparison and/or multiple treatment comparison*

No indirect comparison of multiple treatment comparison was supplied in the CS, except for the comparison of cerliponase alfa trials with the natural history cohort (190-901) which is considered in Section 3.3.

### *3.8 Additional work on clinical effectiveness undertaken by the EAG*

The EAG performed some limited, additional analyses to investigate the validity of the results supplied by the company. As the EAG did not have access to the original trial data we used two sources of data for analysis:

1. Data on ML score over time for each patient in 190-202, 190-203 and MAA FAS cohort, digitally extracted from figures in clinical study reports, or from figures supplied to the EAG for the MAA cohort.
2. Data on changes in MLVS scores (and sub-scales) at each year of follow-up, supplied to the EAG on request for clarification.

The EAG notes that it was therefore not possible to completely replicate the company's analyses. In particular the EAG notes that all trial patients are included in its analysis, and not just those matched to patients in the natural history cohort; and also, that the FAS data (i.e. all patients) was used from the MAA cohort, as individual-level data was not supplied separately for new starters.

Using the individual-level data on ML score we plotted the mean decline in score over time according to ML score at treatment initiation (see Figure 7). These results are generally consistent with those presented by the company. For patients starting with an ML score of 3 to 5 the rate of decline with cerliponase alfa was around 1 point every 3 to 4 years. Patients starting at ML score 2 may have a slightly slower rate of decline. The small number of patients starting at ML 1 showed no decline in score over time. Patients starting at a ML score of 6 showed no progression in the first 4 years, but the two patients in 190-202 followed up for longer both showed rapid decline in scores in later years.

The EAG performed linear regression analyses of ML score against time on treatment, for each study and for all studies pooled. Results are shown in Table 11. Our analysis suggests a typical decline of around 0.26 points per year, or one point every four years. There was considerable variation across the three sources of evidence, with a notably slower rate of decline observed in trial 190-203. We note that these rates of decline do not match those reported in the CS (see Table 5). The EAG is unable to determine why that should be.

**Table 11 Decline in ML score per year: EAG analysis**

| Trial | Estimated decline in ML score per year | |
|---|---|---|
| | Mean | SD |
| 190-202 | 0.226 | 0.030 |
| 190-203 | 0.083 | 0.040 |
| MAA | 0.334 | 0.075 |
| All trials pooled | 0.255 | 0.034 |

Linear regression analyses also found some inconclusive evidence that patients starting with a ML score of 6 may have slower disease progression, by 0.11 points per year (p-value 0.082). However,

given the limited data, and the suggestion of a non-linear trend in Figure 7, this finding should be interpreted with caution.

**Figure 7 Mean decline in ML score over time, by score at baseline**

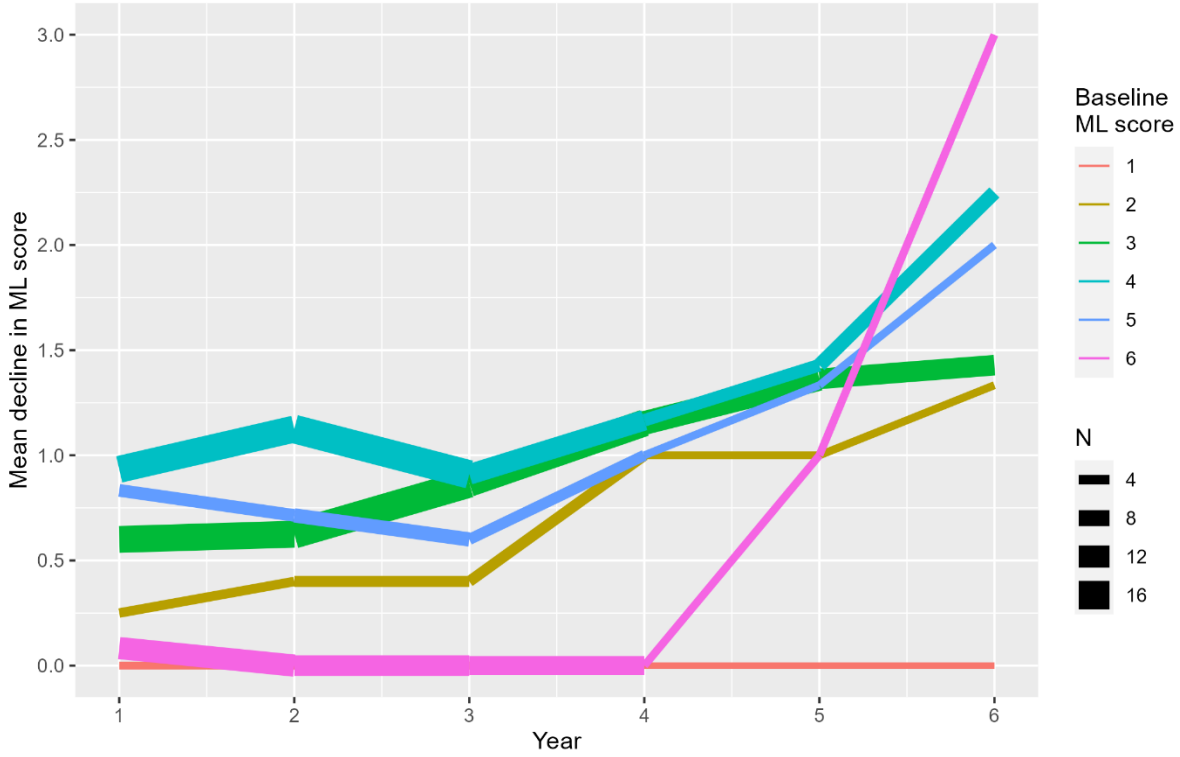



Figure 8 shows the Kaplan-Meir curve for a 2-pont decline in ML score (this are not necessarily "unreversed" declines) separately for each of the three study cohorts. Trial 190-202 and the MAA cohort are consistent, with around 50% of patients having a 2-pont decline in ML score within 5 years. The 190-203 trial has notably slower decline. This highlights the EAG's concern that the 190-203 trial might not be representative of typical patients treated with cerliponase alfa (see also Section 3.2.1.1).

**Figure 8 Time to a 2-point decline in ML score, by study**

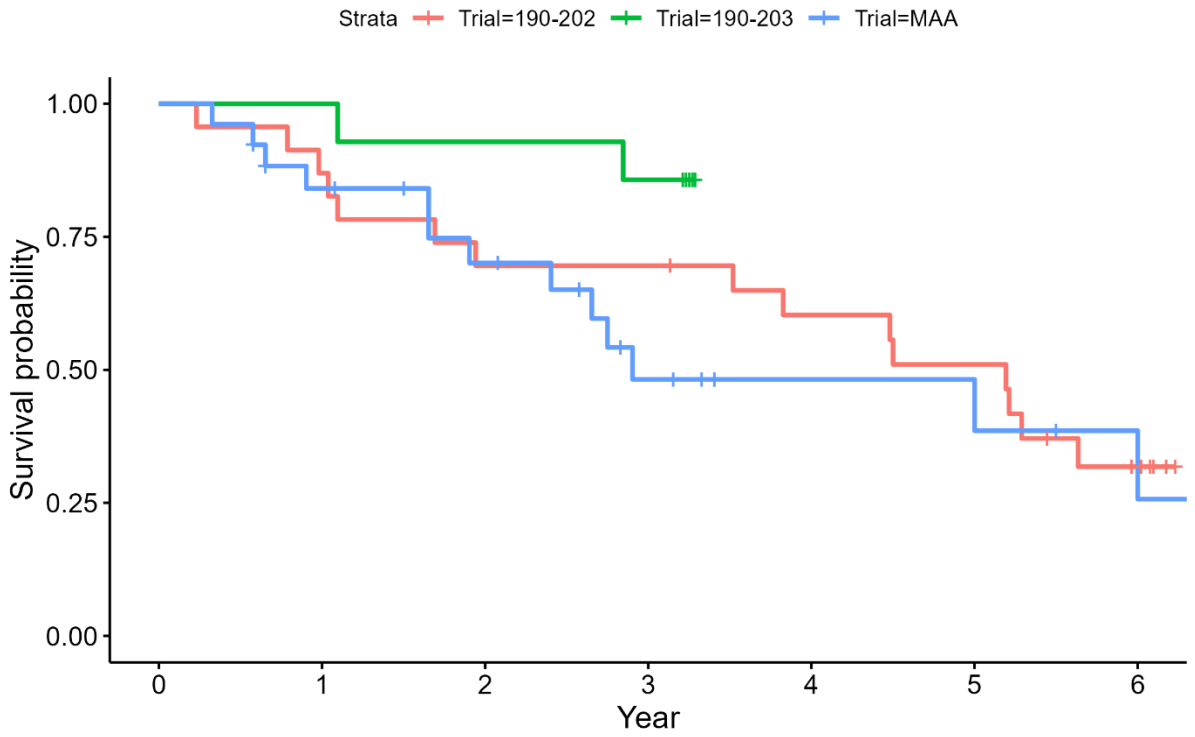
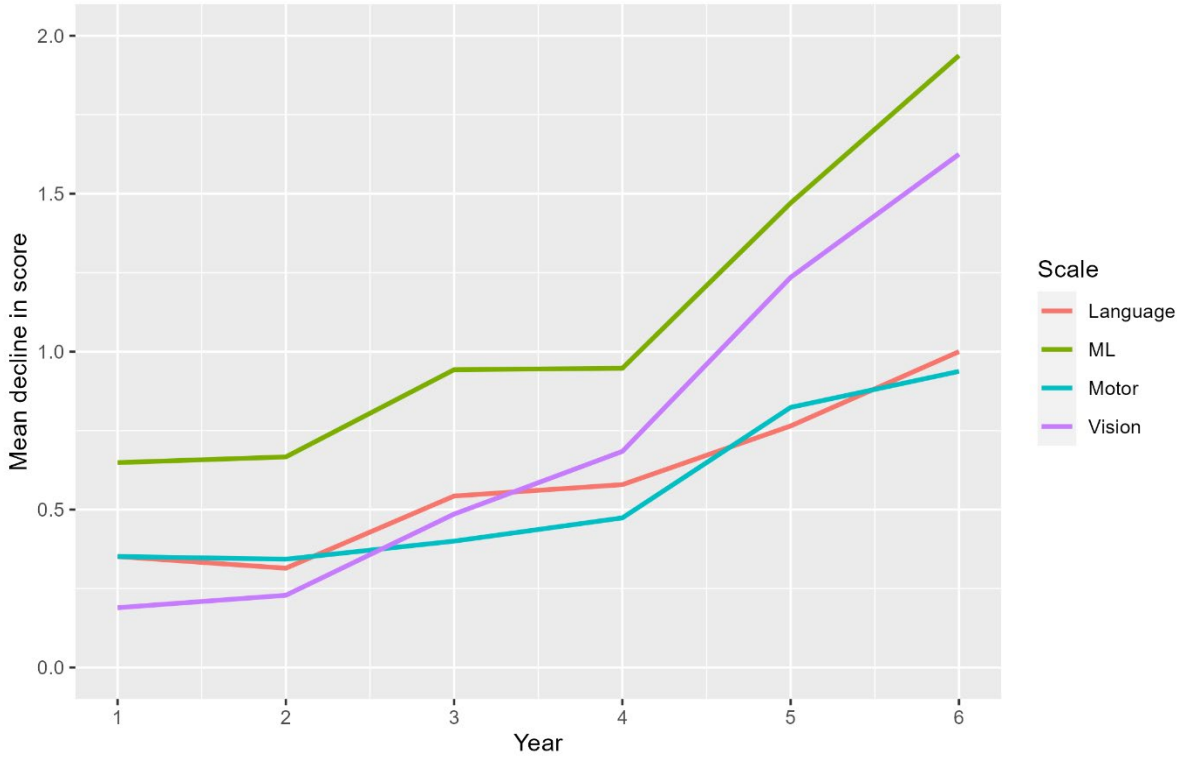



Figure 9 shows the predicted decline in scores over time for ML score, and motor, language and vison sub-scales of MLVS, using the tabulated data supplied by the company. For ML score this is consistent with Figure 7, with a decline of about 1 point every 3 years. Motor and language score both show predicted decline of 1 point about every 6 years. Unlike the results in Section 3.3.3, motor and language scores appear to decline at the same rate. These are consistent with a combined loss in ML score of 2 points every 6 years. Vison loss is more rapid, at around 1 point after 4 or 5 years.

**Figure 9 Decline in motor, language and vision scores over time**




### *3.9 Conclusions of the clinical effectiveness section*

Evidence from the natural history cohort (190-901) shows that, without cerliponase alfa, patients with CLN2 lose language ability, motor function and vision very rapidly. All patients declined by at least two points on the CLN2 ML scale within three years, or were censored. Patients will have complete or substantial vison loss within four years. Around 30% to 40% of patients will die within 6 years of diagnosis.

Evidence from the two cerliponase alfa trials (190-201/202 and 190-203) and the managed access cohort shows conclusively that treatment with cerliponase alfa slows disease progression. Kaplan-Meier analysis suggested that only around half of patients are expected to decline by two or more points on the CLN2-ML scale within 5 years, with very few having a decline to a score of zero. The data suggest a typical rate of decline in ML score might be around 1 point of decline every 3 or 4 years, with about a 1 point decline every 6 years in each of motor function and language separately. The EAG notes, however, that this is unlikely to be a smooth decline over time, and patients may experience long periods of stability or periods of rapid decline. The rate is also likely to be very variable across patients.

The EAG notes that the evidence points to cerliponase alfa slowing disease progression, but not halting that progression. The EAG therefore disagrees with the statements made in the CS that cerliponase alfa leads to “stabilisation” of disease. As follow-up has not extended beyond six years for

most patients, the long-term prognosis is uncertain. The EAG suggests that, given current evidence, it should be assumed that patients will continue to decline to an ML score of zero over time, but the slow rate of decline means that patients are likely to survive into early adulthood.

There is some evidence that patients who start treatment at younger ages, and before motor function or language ability deteriorates, may benefit more from treatment. No patient with an ML score of 6 at treatment initiation had any decline in scores within three years. However, the two such patients with longer follow up did experience some decline in ML score after three years. It is therefore possible that cerliponase alfa may postpone decline for some years, or lead to a slower decline, in patients who start treatment at ML score 6. However, given the small numbers of patients involved and the short follow-up times, this is not certain. It is also possible that, because patients diagnosed at ML score of 6 are likely to be younger at time of diagnosis, the slower rate in decline in these patients is at least partly attributable to the fact that decline would not start immediately, even without cerliponase alfa treatment.

Evidence on vision, using the vision subscale of the overall CLN2 MLVS scale, suggested that cerliponase alfa might slightly delay vision loss, perhaps by a few years, but that cerliponase alfa is unlikely to prevent vision loss in the longer term. The limited data on other vision measurements presented supported the conclusion that the treatment does not prevent long-term vision loss.

Evidence on seizures was limited, and mostly drawn from the seizure subscale of the overall CLN2 MLVS scale. Those data suggested that cerliponase alfa may help reduce number and severity of seizures, as there was no apparent decline in MLVS seizure score over time on cerliponase alfa. However, the company supplied only very limited data on number and severity of seizures over time, so the full impact of cerliponase alfa on seizures is uncertain. Anecdotal evidence supplied by the EAG's clinical adviser was that patients experience fewer, less severe seizures, and with less need for hospitalisation.

Evidence on other clinical outcomes, particularly non-neurological outcomes, was too limited to draw any firm conclusions. Data on natural history patients was not available for any non-neurological outcome (except vision), so whether cerliponase alfa improves any of these outcomes is unclear.

The company's submission was incomplete in that it did not report HRQoL results for studies 190-203 and 190-801 and the reporting of results data for other studies was sometimes limited. The reliability and clinical validity of the HRQoL data which were reported appears highly uncertain, given the tendency for HRQoL scores to remain stable despite declining ML scores.

Cerliponase alfa appears to be generally well-tolerated although the number of treatment-related serious adverse events and device-related adverse events varied widely across studies.

The EAG therefore concludes that use of cerliponase alfa does slow the progression of CLN2, particularly slowing the decline in motor function and language ability, but it does not appear to halt this decline. It appears to reduce the number and severity of seizures, but evidence on this is limited. It does not appear to prevent long-term loss of vision.

### 3.9.1 Areas of outstanding uncertainty

The EAG considers that there are some areas of uncertainty that might affect the long-term clinical impact of cerliponase alfa and its cost-effectiveness. The EAG notes that resolving these issues will require new long-term data collection.

1. Disease progression after long-term use of cerliponase alfa is currently unclear because key trials (190-202 and 190-203) have not yet extended beyond five years of follow-up. Rates of disease progression may vary across patients and within patients, with possible long periods of stability, or periods of rapid decline. How CLN2 might progress when patients reach more severe states (e.g. ML state 1 or 2) is uncertain. Continued long-term follow up of patients is required as disease progresses.

2. Patients who start treatment at younger ages and with limited, or no, disease progression (ML score of 6) might have a long period before disease progresses, or have slower disease progression. However, the number of patients with an ML score of 6 at treatment initiation is small, and most have limited follow-up, so their disease progression is uncertain. Further follow-up is needed of patients who started treatment with an ML score of 6, including recruiting more of such patients to the MAA.

3. Data from the CLN2 MLVS scale suggests that cerliponase alfa may be helping to prevent seizures or reduce their severity. However, this scale provides limited information on the clinical impact of seizures, and more detailed data on seizures was not available for most patients. Consequently, the true impact of any seizure prevention on quality of life is uncertain. More detailed future collection of data on seizures is needed, including: number of seizures over time, severity and type of seizures and seizures needing hospitalisation.

4. Evidence on cerliponase alfa was mostly limited to components of the MLVS scale. Evidence on non-neurological outcomes, such as myoclonus, dystonia, and cardiac events, and on quality of life generally, was very limited. If cerliponase alfa extends life, these non-neurological outcomes may have a greater impact on patient health and quality of life as they live longer. Future collection of data on a broad range of outcomes beyond the MLVS scale is required.

# 4 COST EFFECTIVENESS

This section provides a summary of the original NICE appraisal of cerliponase alfa with a focus on the rationale for reappraisal and relevant evidence developed since, an overview of the company's economic analysis of cerliponase and its critique by the EAG.

## *4.1 Previous appraisal of cerliponase alfa for CLN2*

Cerliponase alfa for the treatment of CLN2 was previously appraised by NICE in 2019, with a positive recommendation conditional on a MAA. [29] The MAA allowed giving patient access to cerliponase alfa, while reducing the financial risk to the NHS given the cost of the technology.

The two key areas of uncertainty in the previous appraisal were:

i. long-term disease stabilisation assumptions for patients treated with cerliponase alfa;
ii. The baseline distribution across health states defined by ML scores which was expected to shift towards higher scores in NHS clinical practice compared to what had been observed in the company's clinical study programme, due to earlier diagnosis.

These two areas of uncertainty were also the key drivers of cost-effectiveness for cerliponase alfa compared to the SoC. The NICE committee noted that data collection could reduce uncertainty on the following elements:

- CLN2 clinical rating scores over time;
- Frequency and severity of tonic-clonic seizures;
- Myoclonus and dystonia control;
- Visual acuity;
- Extra-neurological symptoms (resulting from accumulation of lipofuscin in organs such as heart, pancreas and liver);
- Cause of mortality;
- Improvements in CLN2 scores at diagnosis due to earlier diagnosis and active treatment (i.e., cerliponase alfa) availability in the context of MAA;
- Measures of quality of life.

Since the original HST12, the clinical efficacy and safety evidence has developed through both increased follow-up of existing studies and new studies being conducted (please see detail of these studies in Section3.2). Of these studies, the EAG highlights the following as potentially relevant to the updated company's economic analysis:

- Study 190-201/202, the key source of effectiveness in HST12 (96-week follow-up), has completed its follow-up (280 weeks on study);
- The post-marketing study 190-203 was completed (169 weeks follow-up) - this was a study which aimed to develop clinical evidence in younger patients, including those younger than 2 years old;
- MAA data collection including patients previously treated with cerliponase alfa in the company's clinical trial and new starters in the NHS (209 weeks follow-up);
- First wave of study 190-801, which aimed to assess changes in frequency and severity of seizures and seizure complications, as well as the onset, frequency and severity of movement disorders in patients treated with cerliponase alfa.

The company's cost-effectiveness model is an updated version of the economic model used by the company in the original HST12, which incorporates some of the newly developed clinical effectiveness data. The company's lists in page 128 of the CS the elements of the cost-effectiveness model which have been updated for the current reappraisal of cerliponase alfa in CLN2. The EAG has summarised in Table 12 the key features of the CS and evidence sources which have been updated in the economic model in relation to the original HST12 (as per the NICE committee preferences). The EAG presents further details on the differences between the original appraisal and CS for reappraisal in the subsequent sections of the EAR, as signposted in Table 12.

**Table 12 Comparison of key features and evidence sources of the original HST12 and current CS**

| | HST12* | Evidence* | CS | Evidence | Section of the EAR |
|---|---|---|---|---|---|
| **HS baseline distribution** | HS1: 50%; HS2: 50% | NICE committee's preference | HS1: 87.5%; HS2: 12.5% | Study 190-203, under 3 years old subgroup | 4.2.4 |
| **Stabilisation assumptions** | 'Early stabilisers' are assumed to remain in the same health state from 16 weeks until the end of the model time horizon<br>Remaining patients are assumed to progress at a rate of 1 point on the ML scale beyond 16 weeks and for the rest of the model's time horizon. | Study 190-201/2, 96 weeks follow-up | Patients starting treatment in health state 1 (ML score of 6) remain in this state for the first 6 years.<br>After this, these patients are assumed to transition between health states at half the rate observed for patients initiating treatment in other health states | Study 190-203 | 4.2.7.1 |

| | | | | | |
|---|---|---|---|---|---|
| **Transition probabilities HS1-7** | Assumed constant rate of events between specified time points | Study 190-201/2, 96 weeks follow-up matched 1:1 to Study 190-901 | Estimated with MSM R package | Study 190-203 matched 1:1 to Study 190-901 | 4.2.7.1 |
| **Progressive symptoms** | Symptoms included: distress; dystonia; myoclonus; requirement for a feeding tube.<br><br>Treatment effect applied to seizure related resource use only | Clinical opinion: Delphi panel, 2016 [30] | Symptoms included: distress; dystonia; myoclonus; requirement for a feeding tube; musculoskeletal pain.<br><br>Treatment effect applied to all progressive symptoms resource use, except epilepsy | Clinical opinion: Company's advisory boards [31, 32] | 4.2.7.3 |
| **Vision loss** | Informed by SoC for both treatment groups | ERG's base-case assumption | Linear progression to complete vision loss between 6 and 20 years of age for both cerliponase alfa and SoC in health states 1–6, and vision loss assumed for all patients in health states 7–9 | Clinical opinion | 4.2.7.4 |
| **Non-general population mortality** | Disease specific (HS9 only) and neuro-disability related mortality included | Company's scenario analysis informed by a study in TBI | Disease specific included (HS9 only) | No deaths observed in cerliponase alfa trial programme in which neuro-disability was the cause | 4.2.7.5 |
| **Adverse events** | ICV device related infections included | Published literature | ICV device related infections excluded and replacement of ICV device assumed to occur every 4 years | Not justified in the CS, but clinical opinion to the company suggested lower rates of infection than previously observed | 4.2.9 |
| **Treatment discontinuation** | At HS7 | Company's base-case assumption | At HS6 | Not justified in the CS | 4.2.8 |

| | | | | | |
|---|---|---|---|---|---|
| **Caregivers/sibling utilities** | No treatment effect | Company's base-case assumption | 50% lower disutility at each HS for the cerliponase alfa treatment group compared to SOC. | Clinical opinion | |
| Costs of ECG monitoring | Included for patients treated with cerliponase alfa: i) every 6 months for all patients; ii) at every infusion for those with a history of bradycardia, conduction disorders, or structural heart disease. | ERG's base case assumption | Excluded | Not justified in the CS | |
| Cost of psychiatric support for behavioural symptoms | Included for patients treated with cerliponase alfa aged 13 years and older | ERG's base case assumption | Excluded | Clinical opinion | |

*Assumptions and evidence sources used to inform decision making

**Abbreviations:** CS, company submission; ERG, evidence review group; HS, health state; SoC, standard of care; TBI, traumatic brain injury.

## *4.2 EAG comment on company's review of cost-effectiveness evidence*

### 4.2.1 Summary of company's review of existing economic studies

Appendix G of the CS reports an SLR to identify cost-effectiveness studies for patients with confirmed CLN2 disease or TPP1 deficiency. The searches were an update conducted in January 2024 of the company's SLR (conducted in January 2017) in the original submission to NICE for the appraisal of cerliponase alfa to treat CLN2 (HST12). Some the search strategies were included in Appendix G (page 6-24). In response to the EAG's PfC, a further document was provided by the company (see response to C1-3, PfC), which included explanations for errors identified by the EAG. The EAG's appraisal of evidence identification to inform this SLR is presented in Table 45 (Appendix 2).

Study inclusion and exclusion criteria are reported in Table 8 of the CS (Appendix G). In brief, studies were eligible for inclusion in the SLR if the population related to people of any age with confirmed CLN2 disease or TPP1 deficiency, were economic evaluations (except cost analyses and/or cost of illness studies) and published in English.

The company's SLR as updated in January 2024 identified 225 potentially relevant publications, with 201 studies screened on the basis of their title/abstracts after duplicates were removed. Of these 12

publications were screened based on full text plus one additional publication identified via hand searching. The company considered three publications suitable for inclusion (See Figures 1 and 2 in Appendix G of the CS for the company's PRISMA diagram of the original and updated SLR), namely one cost-utility [33] and two HTAs. [34] [35]. The study characteristics and summary of the included cost-effectiveness studies are presented in Table 9 (Appendix G) and Table 36 of the CS, respectively.

***Points for critique***

The EAG considers that the searches were comprehensive and likely to have identified all relevant published cost-effectiveness studies, but might have missed relevant HTA submissions. In addition to the two HTAs[34, 35] included in the company's SLR, the EAG identified two other HTA submissions for cerliponase alfa for the treatment of for treatment of CLN2 disease, which were considered relevant by the EAG.[36], [37]

The company does not describe how the studies identified in their CS were used to inform the economic model used to conduct the cost-effectiveness analysis in the current appraisal. The EAG reviewed previous HTAs and the cost-effectiveness study [33] identified by the company, to identify key assumptions and parameterisation choices across the different models.

The Markov model submitted by the company for the current appraisal is an updated version of the model in the original HST12, and has the same model structure for three other HTAs identified as relevant. [CADTH, NCPE, SMC] [34, 35] The model structure in these previous HTAs includes 10 mutually exclusive health states, of which 9 health states are defined in terms of ML score, vision loss and requirement for palliative care, and the 10$^{th}$ health state corresponds to death (see section 4.2.3, Figure 10). In contrast, the model considered by the Pharmaceutical Benefits Advisory Committee (PBAC), included fewer health states, by not explicitly including health states for vision loss and requirement. The EAG notes that despite the similarities across model structures in the CS and other submissions to HTA bodies, there were a few key features which differed across models and which have the potential to impact on the estimates of cost effectiveness. These features pertained to the:

i. <u>Baseline distribution of patients across health states</u>
ii. The baseline distribution considered to better reflect (current and/or in the near future) clinical practice varied considerably across HTAs, reflecting different views on the impact of cerliponase alfa on early disease diagnosis and treatment initiation.
iii. <u>Transitions allowed between health states defined by ML scores</u>
While the model in HST12 allowed disease improvement (i.e., backwards transitions to a less severe health state defined by a higher ML score) with cerliponase alfa, but not for the SoC, the CADTH committee preferred the assumption that disease improvement is not possible with either treatment group.

iv. Stabilisation assumptions

In all models but one (PBAC did not include any assumptions on stabilisation) the transition probabilities for health states defined by ML scores alone for patients treated with cerliponase alfa differed if individuals were considered to be early or late stabilisers. Early stabilisers corresponded to the proportion of patients for which there was no observed disease progression as evidenced by a decline in ML score beyond the first 16 weeks of treatment with cerliponase alfa in Study 190-201/202 (96 weeks follow-up). Early stabilisers were assumed to remain in the same health state as at 16 weeks for the remainder of the model time horizon, unless they died before. The remaining patients were considered late stabilisers. In HST12[4], late stabilisers were assumed to stop progressing at 96 weeks. The model also considered that 26% of patients were non-stabilisers and remained at the same risk of progression as previously (i.e., in the period between 16 and 96 in the model) throughout the time horizon. In contrast, in the SMC model [35] late stabilisers' transitions were assumed to continue progression at a rate of 1 point on the ML score per 80 weeks until 96 weeks, after which point they remain in the same health state for the rest of the model time horizon.. The National Centre for Pharmacoeconomics (NCPE) also preferred the assumption that late stabilisers would carry on progressing throughout the time horizon.

v. Mortality risks included

In addition to general population mortality, most models include disease related mortality that only applies to patients with a ML score of zero (specifically, the most severe health in all models). [4, 35] Furthermore, these same models consider infections and neuro-disability related mortality.

vi. Health state utilities

Treatment specific health state utilities were applied in all models, with variation on the evidence source used to inform these across HTAs. In two HTA (SMC and HST12), [4, 35] committee preferred health state utilities were derived from EQ-5D-5L questionnaires completed by 8 clinical experts as a proxy for patients experiencing the description in a set of vignettes describing each health state in the model according to treatment group. The estimated EQ-5D-5L utilities were then mapped to EQ-5D-3L. In HST12, an age-adjustment to health state utilities was applied from the point that patients reached 18 years, so as to prevent health state utilities to exceed those of the general population. In two other HTAs, [36],[34] preferred base-case utilities were derived from PedsQL collected in the cerliponase clinical programme studies from either patients or a caregiver proxy were mapped into EQ-5D-3L scores. In the PBAC submission, the company used PedsQL in their base-case, which was accepted by the committee. CADTH preferred PedsQL derived utilities despite considering these not to be ideal due to the use of caregiver proxies. The CADTH committee considered this more appropriate than to use the vignette study, due to concerns around the

use of clinical experts as proxies (including at least one of whom was involved in the development of the study to derive the utilities).

vii. Sibling and caregiver disutilities

Health state specific sibling and caregiver disutilities were also included for the first 30 years in the model for some HTAs, (e.g., SMC and HST12) [4, 35] while they were excluded in others (e.g., NCPE). [37] While sibling and caregiver disutilities varied across health states, these did not differ between treatment groups.

The study by Gutić et al, 2023,[33] applied a discrete event simulation model to assess the cost-effectiveness of cerliponase alfa compared to symptomatic therapy for late infantile CLN2. In this model, disease progression was not driven by changes in ML scores, as in the previous HTAs models (where this was done implicitly given the model structures). Instead, the Gutić et al, 2023,[33]model considered time to key progression related symptoms and events namely epilepsy, abnormal behaviour, falls, dementia, inability to communicate and vision loss. This approach allowed linking disease progression to symptoms of progression other than motor and language function. Given the fundamental differences in modelling approach and structural assumptions between the Gutić et al, 2023 and the HTA models, it is difficult to contrast these models in detail. However, the key difference in the approaches taken to include progressive symptoms is that progression in these other symptoms is inextricably linked to changes in ML scores in the HTA models, while this model allows relaxing this assumption. This feature could be helpful to explore structural uncertainty, but the EAG acknowledges that the link between ML progression and symptoms (except vision loss), has been considered clinically plausible. Furthermore, the Gutić et al., 2023,[33]model is an adaptation of a model developed to assess the cost-effectiveness of alternative treatments for Niemann–Pick disease type C, and it is unclear if the natural history of this lysosomal disorder is similar to that of CLN2.

The treatment effect of cerliponase alfa compared to symptomatic therapy in the Gutić et al., 2023,[33] model was simple delay in disease progression and time to death by 24 months. It is unclear how this delay was informed from the source cited (a review of clinical evidence on cerliponase alfa for late infantile CNL2) and whether the delay applied equally to all progression markers, so this study is of limited relevance to inform the current appraisal.

Another difference between the Gutić et al, 2023,[33] model compared to previous HTAs was this study did not assume different utilities between cerliponase alfa and SoC, so QALY gains (7.28 QALYs over a 40 year time horizon, at a 3.5% annual discount rate) for cerliponase are driven solely by the delay to manifesting progressive symptoms and death.

### 4.2.2 NICE reference case checklist

Table 13 summarises the extent to which the CS complies with the NICE reference case requirements.

**Table 13 NICE reference case checklist**

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers | The CS is appropriate. |
| Perspective on costs | NHS and PSS | The CS is appropriate. |
| Type of economic evaluation | Cost–utility analysis with fully incremental analysis | The CS is appropriate. |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | The CS is appropriate. |
| Synthesis of evidence on health effects | Based on systematic review | The CS is partly appropriate.<br><br>The company's base-case did not apply pooled evidence to inform the cost-effectiveness analysis.<br><br>Scenario analysis relied on pooled data to estimate transition probabilities in health states 1-7. |
| Measuring and valuing health effects | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults. | The CS is partly appropriate.<br><br>Health effects are expressed as QALYs, but treatment specific health state utilities were derived from a vignette study. Clinical experts were asked score each vignette using the EQ-5D-5L questionnaire.<br><br>Directly reported EQ-5D data collected in the effectiveness studies was only available for patients treated with cerliponase alfa. |
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | The CS does not strictly comply with the reference case, as clinical experts were used as proxies for patients.<br><br>EQ-5D data reported directly (and also mapped from PedsQL to EQ-5D-3L) by patients/carers in the effectiveness studies, but only for those treated with cerliponase alfa. |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | The CS is appropriate.<br><br>EQ-5D-5L scores derived for each vignette were mapped to EQ-5D-5L using the Hernández Alava et al. (2020) algorithm.[38] |
| Equity considerations | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | The CS is appropriate. |
| Evidence on resource use and costs | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS | The CS is appropriate. |

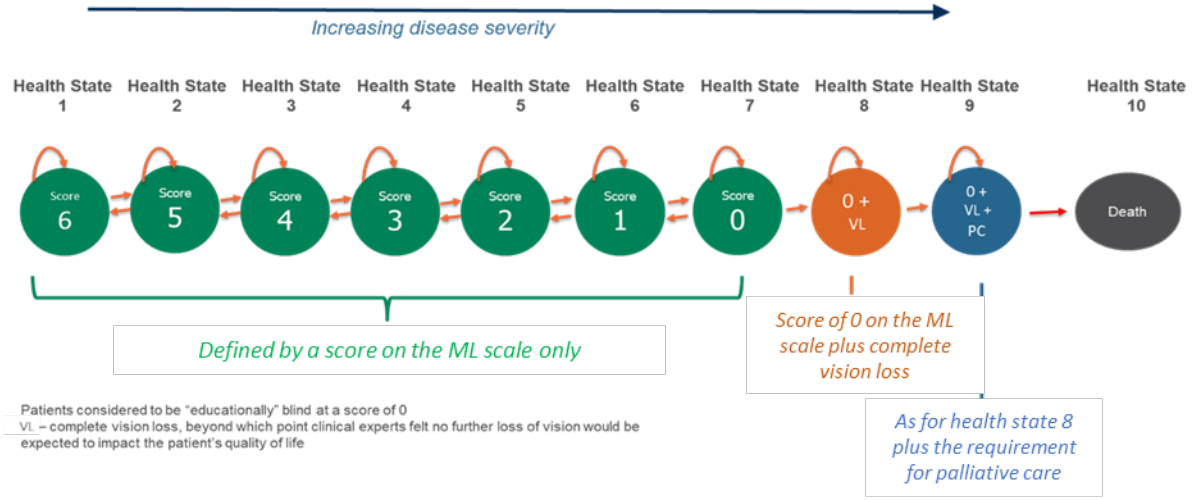
| | | |
|---|---|---|
| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | The CS is appropriate. |
| PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome. | | |

The EAG considers that the CS mostly complies with the NICE reference case requirements.

### 4.2.3 Model structure

The economic model in the CS (see Figure 10) has the same structure as the one in HST12. [4] The model follows a Markov cohort modelling approach, with patient transitions possible at every two-week cycle (with a half-cycle correction applied).

**Figure 10 Model diagram (Figure 18, CS)**




In brief, the model consists of 9 mutually exclusive health states defined by ML score (i.e., the adapted version of the four-domain Hamburg scale measure [20], the CLN2 clinical rating scale, which includes the motor and language domains of the scale and excludes the vision and seizure domains), vision loss and palliative care requirement, to capture the progressive nature of the disease, plus a death (absorbent) state. Severity of disease increases with reduction of ML score from 6 to zero for health states 1 to 7, respectively. Patients in subsequent health states (8 and 9) also have an ML score of zero. Model entrance can be done, in principle, at any of the alive health states, and for health states 1 to 7 the following transitions at each cycle are allowed:

- Remain in the health state;
- Transition to the next more severe health state (e.g., from health state 2 [ML score 5] to health state 3 [ML score 4]);
- Transition to the previous less severe health state (e.g., from health state 3 to 2) – these transitions only allowed for patients treated with cerliponase.

Once individuals transition to health state 8 (ML score zero plus complete vision loss) transition to previous less severe health states are no longer allowed. For all alive health states transitions between non-consecutive health states are not allowed, except transitions to the death state. General population mortality applies to all alive health states and disease specific mortality applies to individuals in health state 9 (ML score plus vision loss and palliative care). Utility and costs vary by treatment received (i.e., cerliponase alfa or SoC) and health state.

Progressive vision loss conditional on age (and independent from progression in health states 1 to 6) has also been considered in the model and has associated costs and disutility. Other progressive symptoms are also included in the model, namely seizures, distress, myoclonus, dystonia, musculoskeletal pain and requirement for a feeding tube. The proportion of patients experiencing these symptoms and/or the frequency of symptoms varies by health state and treatment received, with associated costs. The occurrence of progressive symptoms in the model is not directly linked to disutility. Instead, the impact on HRQoL of progressive symptoms is assumed to be fully captured in the health state utilities.

Individuals treated with cerliponase alfa are subject to a constant risk of adverse events while on treatment, which impact on costs and HRQoL.

The company justifies the selection of the model structure described above as reflective of the chronic and progressive nature of CLN2 disease, and states that the structure has been validated by clinical experts with experience of the disease and cerliponase alfa.

***Points for critique***

As mentioned in section 4.1, the model structure matches that of the models in the original HST12, [4] and has been previously considered appropriate to inform decision making. Nevertheless, the EAG notes that the concerns highlighted in previous HTAs still remain relevant. [34] The disease progression is driven by changes to the combined motor and language score, which implicitly links progression on these domains directly to other key progression markers (developmental issues, seizures, requirement for a feeding tube, and palliative care). Due to this, observed clinical improvements and delay to progression as informed by the ML score result translate into impacts on other progression markers and into a survival benefit. While this linkage may be clinically plausible for some symptoms (e.g., clinical advice to the EAG suggests that losses in language function may accelerate developmental issues), the implicit magnitude of effects is difficult to validate given the empirical evidence available (due to lack of comparative evidence and evidence for cerliponase alfa not being reported by ML score – see section 4.2.7.3). The company relied on clinical opinion to validate the model structure and inform the effect of cerliponase alfa on progressive symptoms by health state, whereas the transition probabilities for health states 1-7 are based on observed changes in ML scores in Study 190-

203 matched to Study 190-901 (see section 4.2.7.1). Thus, a different evidence source was used to inform cerliponase alfa treatment effectiveness on motor and language vs. other progressive symptoms and the association between disease progression on motor and language functions and other progressive symptoms as modelled was not as observed in the primary data. The EAG notes that the company's cerliponase clinical trial programmes collected some, limited evidence on vision, tonic-clonic seizures, myoclonus, dystonia and requirement for feeding tube (see Section 3.4.6). The company does not discuss how this evidence supports the structural assumptions in the model, and this evidence is not consistently presented by ML score so the EAG cannot comment on this. The EAG is, thus, considers that the structural link between ML score progression and other progressive symptom is uncertain but clinically plausible. Furthermore, the EAG highlights that the company modelled a treatment effect for cerliponase alfa vs. SoC on the proportion of patients in each health state incurring costs associated with distress, myoclonus, dystonia, musculoskeletal pain and requirement for a feeding tube ( see sections 4.2.7.3 and 4.2.11.8), which is a departure from the assumptions in the original HST12 model, where only seizures were assumed to differ by treatment group. The EAG also notes that as per the original HST12, health state utilities reflect the impact of cerliponase alfa vs. SoC on progressive symptoms as described in the vignette study and not on the proportion of patients used to inform resource (see section 4.2.7.3). This introduces an inconsistency between how cerliponase alfa on progressive symptoms is modelled to impact on costs and health-related quality of life (HRQoL).

**Issue: The impact of the link between disease progression in terms of motor and language symptoms and progression in other disease symptoms, as well as the treatment effect of cerliponase alfa on the latter symptoms, are uncertain and difficult to validate, based on the evidence presented by the company. Furthermore, the treatment effect of cerliponase alfa on progressive symptoms is modelled in an inconsistent way between costs and HRQoL impacts.**

### 4.2.4 Population

The company defines the modelled patient population as patients with confirmed diagnosis of CLN2 disease; no population subgroups were evaluated in the cost-effectiveness analysis.

The baseline characteristics of the population in the company's base-case and scenario analyses are summarised in Table 14. The EAG notes that the model simultaneously updates starting age and distribution when the evidence source is selected, implying an intrinsic link between age at treatment initiation and baseline distribution across ML scores.

**Table 14 Baseline characteristics in the economic model**

| Analysis and source | | Base case Study 190-203, <3 years (N=8) | Scenario Study 190-203 (N=14) | Scenario MAA new patients (N=24) |
|---|---|---|---|---|
| **Starting age (years)** | | 2.00 | 3.07 | 4.76 |
| **Proportion of males** | | 50%* | | |
| **Distribution of patients at model entrance (baseline)** | | | | |
| **Health state** | **ML score** | | | |
| 1 | 6 | 87.5% | 50.0% | 18.2% |
| 2 | 5 | 12.5% | 7.1% | 13.6% |
| 3 | 4 | 0.0% | 21.4% | 45.5% |
| 4 | 3 | 0.0% | 7.1% | 13.6% |
| 5 | 2 | 0.0% | 7.1% | 9.1% |
| 6 | 1 | 0.0% | 7.1% | 0.0% |
| 7, 8, 9 | 0 | 0.0% | 0.0% | 0.0% |

* CLN2 disease affects males and females equally, based on clinical expert opinion
**Abbreviations:** MAA, managed access agreement.

The company's preferred evidence source to inform the starting age and patient distribution in the model is the subgroup of patients younger than 3 years old from study 190-203, because they expect this to be more reflective of the patients who will receive cerliponase alfa in the near future. The CS does not specify what is meant by 'near future'. The company further suggested that it is anticipated that starting age will be lower and ML score at treatment initiation will be higher on average than in the full cohort in study 190-203 and the MAA new patient cohort (i.e., MAA patients who did not transition from the cerliponase alfa clinical trial programme), due to:

Earlier diagnosis of the disease;
Shorter interval between diagnosis and treatment initiation;
Role of COVID-19 on delays to diagnosis and treatment initiation.

Furthermore, the company's key source of effectiveness evidence to inform the estimation of transition probabilities (health states 1 to 7) for patients treated with cerliponase alfa is the full patient population of study 190-203. This implies that this population reflects the population in the current appraisal; this issue is discussed in section 4.2.7.1.

The NICE scope for this appraisal stated that subgroups by stage of CLN2 progression should be considered, if the evidence allows. The company does not present any subgroup cost effectiveness analyses, but highlights that scenarios with alternative baseline health state distributions are considered. The company's justification for not presenting subgroup analyses by stage of disease progression does not seem to explicitly hinge on evidence availability, but rather on cerliponase alfa

being indicated for CLN2 disease at all stages of progression according to the marketing authorisation.

***Points for critique***

The distribution of patients at the initiation of treatment is alongside the assumptions on initial stabilisation, the most important cost-effectiveness drivers for cerliponase alfa. This is in part due to the progressive and irreversible nature of CLN2 disease, but also because of the company's assumption of initial stabilisation for patients who initiate treatment with cerliponase alfa in health state 1 (ML score of 6). The initial stabilisation assumption means that these patients are not at risk of progression for the first 6 years in the model and then progress at a slower rate for health states 1-7 than patients who initiate treatment at lower ML scores (see section 4.2.7.1). The baseline distribution is an area of uncertainty, given how diagnosis of CLN2 disease is made currently in clinical practice and how this is changing over time.

Study 190-203 aimed to recruit, at least in part, younger patients and at an earlier stage of progression compared to those in study 190-201/202. The mean age at disease onset and at first seizure (2.1 years (SD 0.72) and 3.0 (SD 0.49), respectively) of the 14 patients in study 190-203 was informed by 7 observations (see table 16, Appendix O of the CS). It is possible that the remaining 7 patients did not contribute information to these estimates, because disease onset had not occurred at the time of enrolment and treatment initiation. The EAG also notes that according to the CSR, [redacted].[11] According to the clinical adviser to the EAG, diagnosis at an ML score of 6 is only likely if i) the child has an older sibling who has previously been diagnosed with the disease, ii) newborn screening for CLN2 is routinely conducted, or iii) the patient had very early onset of seizures. Given the that 7 patients did not contribute to the estimate of mean age at disease outset, recruitment target of the study, and the number of pre-symptomatic patients in the study, the EAG considers that the full patient population in study 190-203 (company's scenario analysis) and particularly, the subgroup of patients younger than 3 years (the company's base-case source for baseline distribution and age,) may reflect a patient population younger and at an earlier point of disease progression than patients in clinical practice. Furthermore, the EAG notes that both sources of baseline distribution from study 190-203 (full population, n=14, and subgroup of patients younger than 3 years, n=8) have small sample size, which also contributes to the uncertainty of the baseline distribution estimates.

The EAG considers that the MAA new patients population is also unlikely to be an appropriate source to inform the baseline distribution at treatment initiation, as it may include a number of patients for whom cerliponase alfa was not a treatment option at the time of diagnosis leading to delays in

treatment initiation. Furthermore, the EAG also acknowledges that COVID-19 may have had an impact on delays to diagnosis and treatment initiation for the MAA new patients population, which are not expected to affect future patient cohorts.

Clinical advisers to the company considered that there is still lack of awareness of CLN2 amongst general practitioners, which contribute to delays to diagnosis in clinical practice.[31] Another factor contributing to diagnosis delays is that current clinical guidance indicate neurology referrals only after some motor and language function deterioration. They also suggested that *"newborn screening for CLN2 is conceivable within the next 5 years"*.[31] If newborn screening was in place, the likelihood of patients being diagnosed at ML score of 6 would be high (with one expert considering 'all patients' would be diagnosed at this score). However, it is uncertain whether newborn screening for CLN2 will be routinely conducted in the near future.

The NICE appraisal committee for the original HST12, preferred the assumption that patients initiating treatment with cerliponase alfa would be equally distributed between health state 1 and 2 (ML score 6 and 5, respectively), as the committee thought this could reasonably achieved in the near future. Other HTA agencies preferred less optimistic baseline distributions (see Table 15), including the SMC, which appraised cerliponase alfa in 2020. The clinical adviser to the EAG considered that the baseline distribution used in HST12 is not yet observed in current clinical practice, nor is it likely to correspond to the expected distribution within the next 5 years. Clinical advice to the EAG suggests the following baseline distributions:

- Current clinical practice: 15%, 45%, 30% and 10% at health states 1, 2, 3 and 4, respectively.
- Clinical practice in five-year time: 50%, 35%, 12.5% and 2.5% at health states 1, 2, 3 and 4, respectively.

The EAG explores this issue further in section 6 using alternative baseline distributions as suggested by our clinical adviser, as well as the NICE committee preferred assumption for these parameters in the original HST12.

**Table 15 Baseline distribution of patients in previous HTAs**

| | | **Distribution of patients at model entrance (baseline)*** | | | |
|---|---|---|---|---|---|
| **Health state** | **ML score** | **Original HST12** | **CADHT 2018** | **NCPE** | **SMC** |
| 1 | 6 | 50% | 34% | As per Study 190-201/202** | 80% |
| 2 | 5 | 50% | 33% | | |
| 3 | 4 | 0% | 33% | | NR |
| 4 | 3 | 0% | 0% | | |

| | | | | | |
|---|---|---|---|---|---|
| 5 | 2 | 0% | 0% | | |
| 6 | 1 | 0% | 0% | | |
| 7, 8, 9 | 0 | 0% | 0% | | |

*Values used to inform decision making; **Actual values not reported; **Abbreviations:** ML, motor language; NCPE, National Committee for Pharmacoeconomics, SMC, Scottish Medicines Consortium

The EAG recognises the evidence challenges in conducting subgroup analysis when the available data sources have very small sample sizes. However, the EAG does not think that scenarios with alternative baseline health state distributions allow a full exploration of the potential impact of heterogeneity of treatment effect conditional on stage of disease progression at treatment initiation on the estimates of cost-effectiveness. The company explicitly modelled this heterogeneous treatment effect to some extent through the initial stabilisation assumption (see section 4.2.7.1). The EAG notes that, although the marketing authorisation allows for treatment with cerliponase alfa regardless of ML score, this does not mean that the estimates of cost-effectiveness of cerliponase alfa will be similar for patients who are treated at different stages of disease progression. The EAG does not conduct further analyses to explore this issue further, because of the evidence limitations noted above which would make any findings very uncertain.

**Issue: Baseline distribution of patients in the model is a key cost-effectiveness driver and area of uncertainty. Company's preferred distribution may be overly skewed towards higher ML scores given current and future clinical practice, according to clinical advice received by the EAG.**

### 4.2.5 Interventions and comparators

The intervention is cerliponase alfa in addition to the SoC and the comparator is SoC. Patients who discontinue treatment with cerliponase alfa are assumed to be treated with SoC for the remainder of the time horizon.

### 4.2.6 Perspective, time horizon and discounting

The cost perspective is that of the NHS and Personal and Social Services, while the HRQoL perspective includes patients, carers and siblings. The company's base case analysis uses a time horizon of 98 years, to allow capturing the impacts on costs and benefits by age 100 years. Since the time horizon is linked to patient starting age, this parameter changes when scenario analysis on the patient baseline characteristics are changed in the model. Costs and benefits are discounted at an annual rate of 3.5% in accordance with NICE guidance.

### 4.2.7 Treatment effectiveness and extrapolation

Treatment clinical effectiveness of cerliponase alfa compared to SoC has been modelled through:

i. Treatment specific health state transitions for health states (health state 1 to 7) and via this a delay to exposure to disease specific mortality;
ii. Treatment specific impact on progression symptoms across different health states (proportion of patients presenting with myoclonus, distress, dystonia, requirement for a feeding tube and musculoskeletal pain; number of seizures and number of seizures requiring rescue medication.

Other elements of clinical effectiveness discussed in this section and on which cerliponase alfa is assumed to have no direct impact on cerliponase alfa compared to SoC include vision loss and disease specific mortality.

Direct treatment effects (i.e., not modelled via the clinical effectiveness estimates which drive transitions between health states in the model) on HRQoL and resource use are described in sections 4.2.10.2 and 4.2.11.3, respectively.

#### 4.2.7.1 *Transitions in health states 1-7*

The company's base case analysis uses data from study 190-203 (n=14) to derive transition probabilities in health states 1 to 7 for patients treated with cerliponase alfa. The company states that the use of study 190-203 as evidence source for the transition probabilities is to align with the starting population in the model and that this population was considered to most closely reflect the population of patients who would receive cerliponase alfa in the 'near future'. The company noted that there are insufficient data to inform transitions based only on patients from Study 190-203 who initiated treatment at age less than 3 years (the patients who informed the starting population in the model - see section 4.2.4), so transition probabilities were derived instead from the full Study 190-203 population.

The company assumed that the proportion of patients who enter the model in health state 1 (ML score 6) are initial stabilisers and <u>all</u> remain in health state 1 (unless they die) for the first 6 years in the model. Beyond 6 years, the transitions in health states 1 to 7 for stabilisers occur at half the rate of the transition probabilities applied to those who enter the model in the remaining health states (i.e., non-stabilisers). A 50% (progression) multiplier was, thus, applied to the transition probabilities of non-stabilisers to derive the corresponding transition probabilities for the initial stabilisers. The company notes that of the 8 patients aged 3 years and younger in study 190-203, 5 patients had further follow-up in study 190-504. Of these patients, those who had a ML score of 6 at baseline in Study 190-203 and a follow-up of 6 years across studies had no changes in ML score in that period. Furthermore, any observations of transitions from ML score 6 in Study 190-203 are stated by the company to reflect

data for patients who started with ML score 5 and experienced fluctuations between ML score 6 and 5 (follow-up duration over which this was observed is not mentioned in the CS). The EAG notes that data presented in Study 190-203 CSR (and reproduced in Figure 11)[11] suggests that [redacted]. It is unclear to the EAG how the company's statement relates to the observed data.

The company's stabilisation assumptions in the current appraisal differ from those preferred by the NICE committee in the original HST12, which allowed for disease progression at the start of treatment with partial stabilisation at 16 weeks. Partial stabilisation was implemented by assuming that a proportion of individuals treated with cerliponase alfa were stabilisers regardless of initial health state (corresponded to the proportion of those for whom there was no observed progression during the 96 week follow-up of Study 190-201/202) and the remaining 26% patients remained exposed to risk of progression throughout the time horizon (see section 4.2.1). This assumption was informed by observations over the 96-week follow-up of Study 190-201/202 and reflect the NICE committee preferences. The company states in response to PfCs that the stabilisation assumptions were updated in the current CS as it is no longer expected that all cerliponase alfa patients will stabilise irrespective of starting state (given data collection since the original HST12).

The company explored uncertainty on the stabilisation assumption with cerliponase alfa in scenario analyses, where the following alternative assumptions are tested:

- 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.

For patients treated with SoC, patients in study 190-203 were matched 1:1 to patients in study 190-901 (see section 3.2.1 for study details); SoC transition probabilities were estimated using data for the subset of matched patients from study 190-901. No stabilisation assumptions were considered for patients treated with the SoC. Patients who discontinue treatment with cerliponase alfa are assumed to have the same transition probabilities as patients who are treated with SoC from the moment they transition further (e.g., when discontinuation is assumed to occur at health state 6, the transition probabilities of SoC apply from health state 7 and onwards).

The company also conducted scenario analyses applying transition probabilities derived from:

i. All patients from studies for cerliponase alfa (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. The MAA database included the five patients who transitioned from studies 190-202 (n=2) and 190-502 (n=3), and for which baseline and subsequent assessments were taken

from their respective clinical trial until the end of trial follow-up and the final assessments taken from the MAA.

ii. 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. According to the company, this analysis captures the impact of any delay in the full treatment effect of cerliponase alfa being realised (i.e. such that the treatment effect of cerliponase alfa differs between the initial period following treatment initiation and later periods)..

In addition to the reasons highlighted above for preferring Study 190-203 to inform effectiveness of cerliponase alfa, the company also stated that the 'all patients' data matched was not the preferred data source for these parameters, because:

- Cerliponase alfa was not a treatment option at the time of diagnosis for 'all patients' in the dataset, resulting in delayed initiation of treatment.
- Some patients experienced progression between the end of the expanded access program and the start of the MAA (i.e. in the period in which they were not receiving treatment with cerliponase alfa).
- The impact of the COVID-19 pandemic on delays to diagnosis and treatment in some patients, and on access to ancillary therapies (e.g., physiotherapy).

The EAG notes that, despite this, the pooled data analysis (i) also informed cerliponase alfa probabilities for the base-case for the transitions from health state 6 and 7, as no observations for these transitions were made in study 190-203.

The company justifies excluding Study 190-801 (see Table 3 for study details) as it did not include ML score analysis over time as a primary outcome (and ML scores over time do not seem to have been collected during this wave). [redacted].

The company estimated transition probabilities using the MSM package in R (using a multistate modelling framework) for both treatments using the matched data described above. The method generates transition intensities (i.e., instantaneous rates) which the company converted to transition probabilities assuming a constant rate over time (and an exponential distribution). This methodology has chosen by the company to account for:

- Multiple data sources with differing observation intervals;
- Differing durations of follow-up between patients;

- Transitions that were intermittently observed in time.

The company states that the MSM estimation models converged for all datasets used to inform the economic model and produced plausible estimates. The transition probabilities applied per cycle in the model for patients in health states 1 to 7 are summarised in Table 16. Further details on the methodology used by the company to estimate these transition probabilities are reported in the company's response to PfCs (see response to clarification question B2).

**Table 16 Transition probabilities per cycle in health states states 1–7 (extracted from Table 42 and 43, CS, and electronic version of the model)**

| | | **Base-case** | | | **'All patients'** | | | **Piecewise at 6 months – 'all patients'** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ML score** | **Health state** | **Cerliponase alfa** | | **SoC** | **Cerliponase alfa** | | **SoC** | Cerliponase alfa | | | | SoC |
| | | | | | | | | **Initial stabilisers*** | | **Non stabilisers** | | |
| | | **Initial stabilisers*** | **Non stabilisers** | | **Initial stabilisers*** | **Non stabilisers** | | **<6 months** | **>6 months** | **<6 months** | **>6 months** | |
| 0 to 1 | 7 to 6 | 3.0%** | 6.1%** | | 3.0% | 6.1% | | 3.0% | 3.0% | 6.1% | 6.1% | |
| 1 to 0 | 6 to 7 | 0.8%** | 1.5%** | 7.1% | 0.8% | 1.5% | 7.6% | 0.8% | 0.8% | 1.5% | 1.5% | 7.6% |
| 1 to 2 | 6 to 5 | 1.3%** | 2.7%** | | 1.3% | 2.7% | | 1.3% | 1.3% | 2.7% | 2.7% | |
| 2 to 1 | 5 to 6 | 1.0% | 2.1% | 10.1% | 1.1% | 2.1% | 9.2% | 1.1% | 0.0% | 2.3% | 0.1% | 9.2% |
| 2 to 3 | 5 to 4 | 0.6% | 1.1% | | 0.7% | 1.3% | | 0.6% | 0.0% | 1.1% | 0.0% | |
| 3 to 2 | 4 to 5 | 3.2% | 6.4% | 11.6% | 1.9% | 3.7% | 11.1% | 1.9% | 0.1% | 3.7% | 0.1% | 11.1% |
| 3 to 4 | 4 to 3 | 3.6% | 7.2% | | 1.2% | 2.5% | | 1.1% | 0.0% | 2.2% | 0.1% | |
| 4 to 3 | 3 to 4 | 3.3% | 6.6% | 12.1% | 2.9% | 5.8% | 7.6% | 2.6% | 0.1% | 5.2% | 0.3% | 7.6% |
| 4 to 5 | 3 to 2 | 0.5% | 0.9% | | 0.3% | 0.6% | | 0.3% | 0.0% | 0.6% | 0.0% | |
| 5 to 4 | 2 to 3 | 2.7% | 5.4% | 5.6% | 3.3% | 6.7% | 7.3% | 3.1% | 0.2% | 6.2% | 0.4% | 7.3% |
| 5 to 6 | 2 to 1 | 2.9% | 5.8% | | 1.3% | 2.6% | | 1.3% | 0.0% | 2.7% | 0.1% | |
| 6 to 5 | 1 to 2 | 0.2% | 0.5% | 4.6% | 0.3% | 0.7% | 6.3% | 0.3% | 0.0% | 0.7% | 0.0% | 6.3% |

*, transition probabilities beyond 6 years from treatment initiation; **, assumed the same as for 'all patients' analysis

***Points for critique***

*Initial disease stabilisation*

The company assumption of initial stabilisation for patients initiating treatment in health state 1 is a key driver of cost-effectiveness for cerliponase alfa. The EAG is concerned that the evidence presented by the company is insufficient to robustly support the stabilisation assumptions and notes that the company only explored more optimistic stabilisation assumptions.

The company justifies the assumption of initial stabilisation based on observed data for patients younger than 3 years old in study 190-203, who may have started treatment before disease onset (see section 4.2.4). The company did not comment how the evidence collected in Study 190-202 (which was ongoing at the time of the original HST12 and has since finished its follow-up) supports the initial stabilisation assumption. The EAG notes, however, that [redacted] in study 190-202 (see CSR, [39] Figure 14.2.2.6.1) who had a ML score of 6 [redacted]. In the company's response to clarification, the company provided the mean estimates of time on ML score 6 for patients who started treatment in this health state, which are shown in Table 17. The clinical adviser to the EAG considered that in light of clinical evidence presented by the company, it is not unreasonable to assume that the initial stabilisation persists for 6 years, but the EAG notes that other plausible and more conservative estimates have not been explored by the company.

**Table 17 Time in ML 6 for patients who were baseline ML 6 (adapted from Table 72, response to PfCs)**

| Dataset | Treatment | n | Time in ML 6 (years); mean |
|---|---|---|---|
| 'All patients' matched dataset* | Cerliponase alfa | 8 | 2.80 |
| | Natural history | 8 | 0.79 |
| Study 190-203 cohort matched dataset* | Cerliponase alfa | 5 | 3.21** |
| | Natural history | 5 | 1.05 |

*, only includes patients in the 1:1 matched cohorts; ** full trial follow-up in Study 190-203 and not including follow-up in subsequent studies

The EAG is also concerned that the high proportion of initial stabilisers in the current company base-case (all individuals with a baseline ML score of score 6) may magnify the impact of the stabilisation assumptions on the estimates of cost-effectiveness, given that the 87.5% of patients in the company's base-case assumed to be in ML score of 6 is considered overly optimistic by the EAG and our clinical adviser (see section 4.2.4) . Furthermore, clinical advice to the EAG suggests that it may be too

optimistic to assume that 100% of patients with a starting ML score of 6 will be initial stabilisers, as there may be differences in response to treatment, and that it would be more reasonable to assume that 80% of patients with this starting score are initial stabilisers.

The progression rate of initial stabilisers beyond 6 years is an area of uncertainty given the lack of observed data beyond this time point for patients with a baseline and 6 years ML score of 6. The clinical adviser to the EAG considered the company's assumption of applying a 50% reduction to transition probabilities in health states 1 to 7 of non-stabilisers to derive corresponding transition probabilities for the initial stabilisers clinically plausible. Nevertheless, but, given that the company did not explore a more conservative assumptions for the reduction in progression for stabilisers following 6 years, the impact of this uncertainty on the estimates of cost-effectiveness needs to be explored further.

In section 3.9, the EAG noted that the clinical evidence suggests that cerliponase alfa slows disease progression but does not halt it. Despite the use of the term 'initial stabilisers' the company's modelling of disease progression is consistent with cerliponase alfa delaying this, particularly for the those initiating treatment at an ML score of 6. Assumptions beyond six years, are however very uncertain.

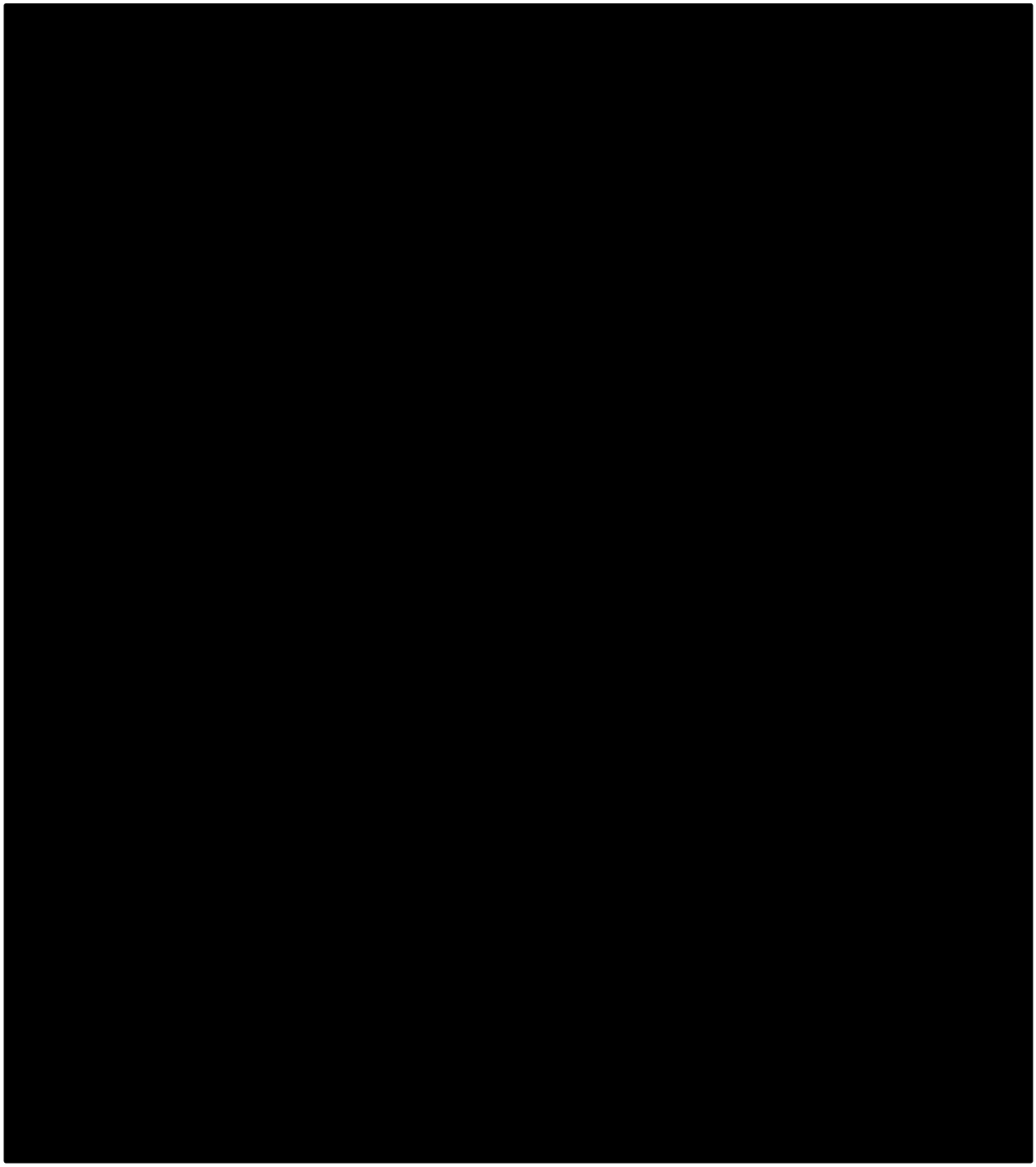
*Selection of evidence sources*

The EAG considers that the company's preferred evidence source to inform the transition probabilities for those treated with cerliponase alfa introduces considerable uncertainty and potential bias favouring cerliponase alfa into the cost-effectiveness analysis. This is in part due to its small sample size (n=14) and, importantly, to the concerns highlighted in section 4.2.4 that the population of Study 190-203 may not reflect patients treated in current and near future clinical practice. While the EAG acknowledges that the 'all patients' pooled data may also introduce bias against cerliponase alfa due to the delays and interruptions to treatment highlighted by the company, this does not justify the exclusion of data from the full follow-up of Study 190-201/202 from the company base-case analysis (15 of the 40 matched cerliponase alfa treated participants. Of the 15, 2 had additional follow-up in the MAA) from the company's base-case, which constitutes a larger of body of evidence and is relevant to this appraisal. In the absence of a scenario analysis where the company estimated transitions probabilities based only on evidence of the company's clinical trial programme, the only way for the EAG to incorporate Study 190-201/202 in their analysis is to rely on estimates from the 'all patients' pooled dataset. The EAG notes that even if a pooled dataset of all clinical trial programme evidence is less affected by delays and interruptions to treatment than the MAA dataset, it may still not reflect the population in NHS clinical practice in terms of baseline distribution across health states at treatment initiation.

*Comparative effectiveness and potential bias*

The uncertainty surrounding the comparative effectiveness data is affected by the use of non-randomised data and the approach taken to match cerliponase alfa and SoC patients. The EAG concerns are in part similar to those highlighted by the ERG to the original HST12 about the matching process and reiterated in Section 3.2.1.3. The EAG notes that it is not clear if the matching approach used to inform the transition probabilities for the SoC is the same as the one described in the clinical section (see Section 3.2.1.3), as this information is not detailed in the company submission. There seem to be differences in how matching was established between patients in studies 190-203 and 190-901 for the purpose of clinical effectiveness (matching described as 3:1 in Section B.2.4.2.1, CS) and cost-effectiveness assessment (matching described as 1:1 in Section B.3.3.2.1, CS). The company did not clearly state in the CS what were the prognostic variables used for matching and the number of patients per treatment group in the matched datasets used to inform the transition probabilities. Matching on a 1:1 rather than 3:1 basis, means that out of three available matches in the 190-901 historic control one in particular was selected, and it is not clear to the EAG how that selection was made and the impact this had on the relative effectiveness of cerliponase alfa vs. SoC (see Figure 11) for the ML scores over time for the cerliponase alfa and matched controls patients over time. The EAG also notes that matching was only possible [redacted].[11] The EAG is, thus, concerned, that the matching approach is not fully characterised and may be a source of bias.

**Figure 11 ML score variation in Study 190-203 matched to Study 190-901 (adapted from figure 14.2.1.1 in the CSR)[11]**



The company does not distinguish in the model between patients with atypical and typical CLN2. In section 2.2.1, the EAG highlights that atypical CLN2, which affects approximately 10% of the population, presents later in life and exhibits slower progression compared to typical CLN2. The proportion of patients with atypical disease in study 190-203, pooled 'all patients' dataset and matched comparator data is unknown. Thus, it is also unknown whether the matching approach allowed balancing the proportion of patients with atypical disease across treatment groups and, if not, what is the likely direction of bias.

*Estimation of transition probabilities*

The method used to estimate transition probabilities for the company's current economic model differs from the one in the original HST12 in two ways:

i. A sophisticated statistical package, which can account for differing follow-up and observation periods between patients and between studies, was used as opposed to estimating transition probabilities by assuming constant rates at specific timepoints in the original HST12.
ii. Transition probabilities were estimate into and from each individual health state (1 to 7), whereas in the original HST12 there was an assumption that transition probabilities would be the same for some health states (1-2, 3-5 and 6-7) due to small number of patients within each ML score.

The EAG requested at PfCs (see clarification question B3) for the number of events and person-time in health state to reflect time at risk for each transition in i) Study 190-203 matched to study 190-901, ii) 'all patients' pooled dataset matched to study 190-901 and iii) study 190-201/202 matched to study 190-901 data cut used to inform the original HST12. This would have allowed the EAG to explore:

- Alternative estimation methods within the timelines available;
- Differences in clinical effectiveness across datasets and investigate whether these differences were driven by the newly developed evidence or by the estimation method.

The company did not present information on patient time at risk in each health state for any of the datasets (only mean sojourn time for study 190-203 matched to study 190-901, 'all patients' pooled dataset matched to study 190-901, as estimated by the MSM package, see Tables 60, 62, 66 and 68, response to PfCs) or any information on study 190-201/202 matched to study 190-901 data cut used to inform the original HST12. The company stated that it was not possible to access the original HST12 dataset in the two-week period, but that this could be done at a later date. Thus, the EAG cannot comment extensively on the differences in the evidence used to derive transition probabilities in the original and current appraisal of cerliponase alfa in CLN2. Nevertheless, the EAG considers uncertain how robust the transition probabilities for health states 1-7 may be to alternative estimation methods, including to the use of different statistical methods to estimate these parameters, and different levels of aggregation for health state transitions (as per the original HST).

The EAG has a few concerns related to the estimation of the transition probabilities for health state 1 to 7. First, the EAG notes the small number of events informing transition probabilities (see Table 18), particularly for the company's base-case preference. The EAG notes that in addition to the observed data described above (from study 190-203, the 'all patients' pooled dataset, and the corresponding matched study 190-901), the company used as an input a single arbitrary initial value

of 0.01 for all transition intensities of those transitions that were allowed in the model; the choice of initial values was not justified by the company. The set of allowed transitions differed depending on the treatment and dataset used. For patients treated with cerliponase alfa only transitions between adjacent ML score defined health states (ML score 0–6; model health states 1–7, and MSM model 0–6) were allowed (i.e., improvement or decline in ML score) when using the 'all patients' dataset to estimate transition probabilities (see Table 31, response to PfCs). When study 190-203 was the source of evidence, the specified transition matrix differed from the one used for the 'all patients' dataset by not allowing transitions from ML score 0 to 1 due to the lack of data informing these transitions (see Table 32, response to PfCs). For the datasets used to inform transition probabilities for the SoC, the transition matrices (Table 33 and 34, response to PfCs) only allow progression between adjacent health states (i.e., improvement to a previous health state was not allowed). Given the small number events used to inform transition probabilities and the use of unjustified and arbitrary initial values as inputs for the MSM models, the EAG is concerned about the extent to which these initial values may be driving statistical model convergence and influencing the derived transition probabilities. Furthermore, the EAG notes that, based on clinical advice, some backward transitions (i.e., transitions to a healthier health state) may be temporary improvements that are not expected to persist, or random variation over time, rather than sustained improvements in the condition. The EAG notes that, by allowing for these backward transitions, some patients treated with cerliponase alfa can over the time horizon transition to increasingly healthier health states, which may not be clinically plausible.

**Table 18 Number of events in each health state (adapted from Table 70 response to PfCs)**

| Transition | **Number of events** | | | |
|---|---|---|---|---|
| | **Company's base-case: Study 190-203 matched to study 190-901** | | **Company's scenario: 'All patients' pooled dataset matched to study 190-901** | |
| | **CA** | **SoC** | **CA** | **SoC** |
| HS7 to HS6 | 0 | 0 | 5 | 0 |
| HS6 to HS7 | 0 | 10 | 7 | 27 |
| HS6 to HS5 | 3 | 0 | 15 | 0 |
| HS5 to HS6 | 2 | 9 | 25 | 29 |
| HS5 to HS4 | 2 | 0 | 16 | 0 |
| HS4 to HS5 | 5 | 8 | 31 | 27 |
| HS4 to HS3 | 5 | 0 | 17 | 0 |
| HS3 to HS4 | 7 | 7 | 30 | 19 |
| HS3 to HS2 | 1 | 0 | 3 | 0 |
| HS2 to HS3 | 2 | 5 | 8 | 11 |

| | | | | |
|---|---|---|---|---|
| HS2 to HS1 | 2 | 0 | 3 | 0 |
| HS1 to HS2 | 2 | 5 | 4 | 8 |

Abbreviations: CA, cerliponase alfa; HS, health state; SoC, standard of care.

Second, the EAG is concerned about the fit of the models applied to estimate the transition probabilities. The estimated models' goodness-of-fit, as illustrated by a comparison between expected and observed health state prevalence (see response to clarification question B2.e), may suggest overfitting of the predicted model outputs to the observed data in some health states, while in other health states the fit appears to be poor. This is particularly the case for the cerliponase alfa-treatment group (see Figure 12 and Figure 13). Therefore, the EAG is concerned about the goodness-of-fit of the statistical models used to estimate the transition probabilities. Despite reporting extensively on the goodness-of-fit of the statistical models (response to PfCs, question B2) used to inform the transition probabilities in health states 1 to 7 in the economic model, the company did not report if any statistical model specifications (and initial values) were assessed and whether better fit could have been achieved.

Third, when modelling the parameter uncertainty of sets of transition probabilities jointly derived with the MSM package in probabilistic sensitivity analysis, the company did not use the respective variance-covariance matrix output to preserve the correlation structure between these parameters. Instead of using a multivariate normal distribution informed by a covariance variance matrix, the company modelled the parameter uncertainty for these probabilities using independent lognormal distributions. The company justified this approach, by saying that it was not possible to use the multivariate normal distribution, as it resulted in negative transition intensities, and that their approach overestimates decision uncertainty. The EAG is concerned that this may suggest instead that the transition intensities estimated by the MSM package are not robust enough.

**Figure 12 Expected prevalence compared with the observed prevalence of each state for the 190-203 patients*(Figure 39, response to PfCs)**

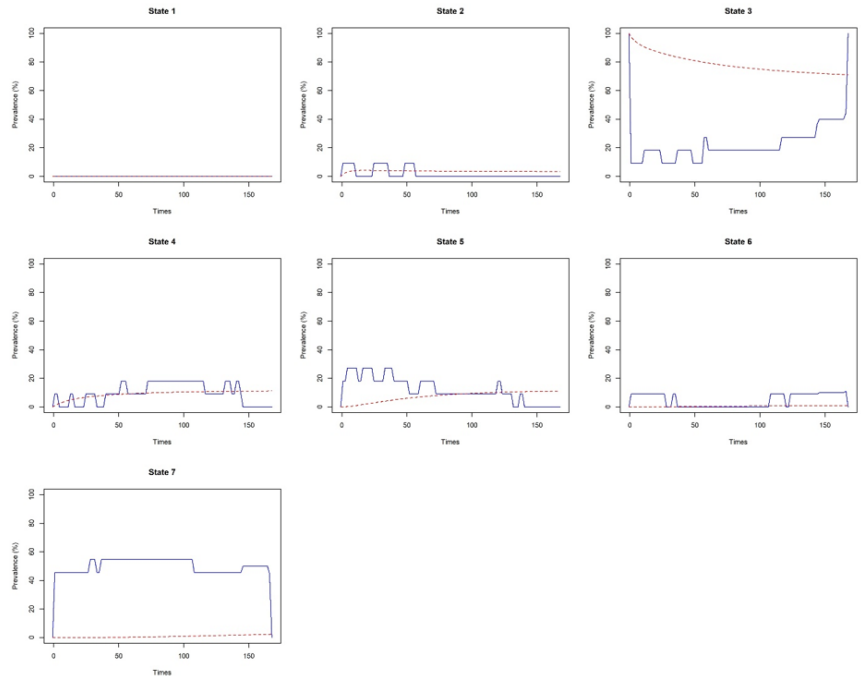
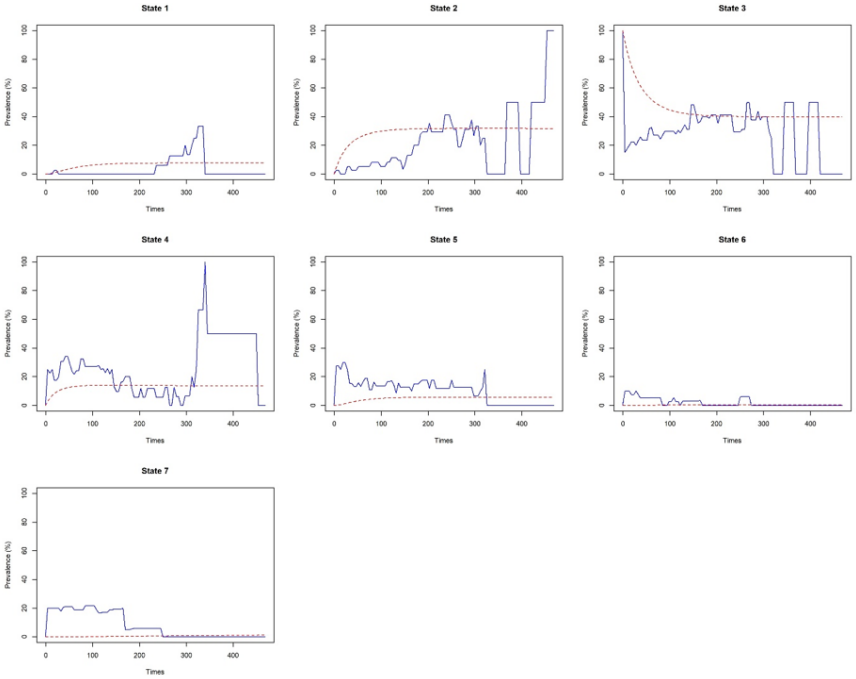



**Figure 13 Expected prevalence compared with the observed prevalence of each state for cerliponase alfa 'all patients'* (Figure 38, response to PfCs)**




*Note that the labelling of health states does not correspond to that used in the CS: State 1 = Health state 7; State 2 = Health state 6; State 3 = Health state 5; State 4 = Health state 4; State 5 = Health state 3; State 6 = Health state 2; State 7 = Health state 1

**Issue: Initial stabilisation assumption for patients treated with cerliponase alfa is highly uncertain despite the additional evidence generated since original HST12 and more conservative assumptions have not been explored.**

**Issue: The company's preferred evidence source to inform the transition probabilities in health states 1 to 7 for patients treated with cerliponase alfa, Study 190-203, may not reflect the population in current and near future clinical practice and be overestimate treatment effectiveness of the technology. Furthermore, Study 190-203 has a smaller sample size and fewer number of events to inform transition probabilities than the 'all patient' dataset.**

**Issue: Comparative effectiveness was established based on a fairly naïve matched comparison in the absence of direct evidence, which is a source of uncertainty and insufficiently characterised by the company in order to comment on the likely direction of bias.**

**Issue: The EAG cannot establish whether the statistic model applied to estimate the transition probabilities for health states 1-7 provides robust estimates for the transition probabilities applied in the model, due to the unclear impact of using arbitrary initial values to inform the MSM models and the potential overfitting of these models to the observed data. Furthermore, the company did not test alternative estimation methods for these transition probabilities, which contributes to the uncertainty around the robustness of these parameters.**

#### 4.2.7.2 *Transitions in health states 7-9*

Transitions beyond health state 7 are independent of treatment group, which the company considers a conservative assumption in the absence of comparative evidence between cerliponase alfa and SoC. Once patients reach health state 8 disease improvement is no longer possible (see Table, 44, CS). These transition probabilities were informed by clinical opinion[30] and are the same as applied in the original HST12. Clinical experts stated that they would expect for patients on standard care to have complete vision loss within one year of reaching a score of zero on the CLN2 clinical rating scale (i.e., on average one year on average for patients to transition from health state 7 to 8), and derived a 2-week transition probability of 3.8% (see section B.3.3.6, CS). The same time to progression between health states 8 and 9 (time from vision loss to requiring palliative care) and 9 and 10 (time receiving palliative care before death) was assumed by the company, and thus the same probability of 3.8% was applied in the model for these transitions.

***Points for critique***

Clinical advice to the EAG considered the transition probabilities in health states 7-9 plausible. The EAG notes, however, that the assumption of no treatment effect on these parameters is not entirely

conservative, as the company assumes that treatment with cerliponase alfa stops once they reach health state 6, but transition probabilities only become the same as for SoC when they transition to health state 7 (see Section 4.2.8). The clinical adviser to the EAG considered that treatment effect would be expected to remain for 6 to 9 months after treatment is stopped. In the company's base case, mean time (undiscounted and half-cycle corrected) in health state 6 corresponds to 3.2 years, so treatment effect for the average patient might have waned before patients even transition to health state 7.

#### 4.2.7.3 *Progressive symptoms*

In line with the original HST12 the company considered in the model the occurrence of progressive symptoms disease distress, dystonia, myoclonus, requirement for a feeding tube and seizures. The company also included an additional progressive symptom to those in the original HST12, musculoskeletal pain, in the CS; the company attributes the inclusion of this symptom to one of the company's advisory boards with clinical experts.[31] The selection of which symptoms to include is informed by Williams et al., 2017, a study on the management of CLN2,[40] and expert opinion.[30, 32 31]

The proportion of individuals assumed to have each progressive symptom (listed in Tables 45 and 47 to 50 of the CS) and the number of annual seizures (Table 46 of the CS) is conditional on the health state and on treatment received. As mentioned in section 4.2.3, this means that progression in terms of decline in ML score drives progression on these symptoms. While symptomatic progression was also driven by ML score changes in the original HST12, the EAG notes (as mentioned in section 4.2.3) that a cerliponase alfa treatment effect was previously applied only to the annual number of seizures. The company did not comment on these differences between the original HST12 and the CS. The EAG summarises the proportion of individuals with progressive symptoms and annual number of seizures in Table 19 and Table 20, respectively, in the original HST12 and in the economic model.

The company assumed that these progressive symptoms would result in consumption of health care resources and costs to the NHS (see section 4.2.11.8), but did not link these directly to impacts on HRQoL (see section 4.2.10.2).

**Table 19 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% |

*Confirmed in the company's model and original data source [31]

**Abbreviations:** CA, cerliponase alfa; CEM, company economic model; HST, highly specialised technology; SoC, standard of care.

**Table 20 Comparison of number of annual seizures in the original HST12 and the company's economic model**

| Health state | ML score | HST12 | | CEM | | | |
|---|---|---|---|---|---|---|---|
| | | Annual seizures (CA) | Annual seizures (SoC) | Annual seizures (CA) | Annual seizures requiring medication (CA) | Annual seizures (SoC) | Annual seizures requiring medication (SoC) |
| 1 | 6 | 1 | 1 | 2.50 | 2.50 | 7.50 | 2.50 |
| 2 | 5 | 1 | 3 | 2.50 | 2.50 | 15.00 | 2.50 |
| 3 | 4 | 1 | 6 | 7.50 | 2.50 | 35.00 | 7.50 |
| 4 | 3 | 1 | 6 | 7.50 | 2.50 | 75.00 | 7.50 |
| 5 | 2 | 1 | 6 | 15.00 | 2.50 | 75.00 | 7.50 |
| 6 | 1 | 1 | 6 | 35.00 | 2.50 | 100.00 | 7.50 |
| 7 | 0 | 0 | 0 | 35.00 | 7.50 | 100.00 | 15.00 |
| 8 | | 0 | 0 | 35.00 | 7.50 | 100.00 | 15.00 |
| 9 | | 0 | 0 | 35.00 | 15.00 | 100.00 | 15.00 |

**Abbreviations:** CA, cerliponase alfa; CS, company submission; HST, highly specialised technology; SoC, standard of care.

***Points for critique***

As mentioned in section 0, transitions between health states is driven by changes in ML score, and, thus, the impact of cerliponase alfa and SoC on motor and language functions as observed in the studies informing the transition probabilities (health state 1 to 7) in the model are translated into impacts on the progression of other symptoms. In addition to the treatment effect of cerliponase alfa on delaying the onset of these symptoms compared to the SoC, the company also applies a within health state treatment effect for the technology informed by expert opinion (three consultants, three senior nursing professionals and one patient representative), as illustrated in Table 19 and Table 20. The EAG notes that one of the objectives of further evidence collection mandated by the NICE committee for the original HST12 was to mitigate the uncertainty surrounding the impact of cerliponase alfa on progressive symptoms (particularly for seizures, myoclonus and dystonia). The company chose to inform these parameters by conducting an unstructured expert elicitation exercise, despite the availability of primary data on seizures, myoclonus and dystonia collected in the company clinical trial programme and the MAA database. It is unclear to the EAG, why the company did not consider these data sources to inform and/or validate the estimates provided by the clinical experts, particularly for patients treated with cerliponase alfa. Furthermore, the EAG reiterates (see section 4.2.3) that it is difficult to validate the approach taken to model the impact of cerliponase alfa on

progressive symptoms, based on the evidence presented by the company. Furthermore, the treatment effect of cerliponase alfa on progressive symptoms stems from both delays to progression compared to SoC, but within health state treatment effects. This further hinders validation, particularly as different sources of clinical evidence (i.e., primary data and expert opinion) are used to inform each element of treatment effect. The EAG is, thus, concerned about potential double counting of effects. Nevertheless, the clinical adviser to the EAG considered that the impact of cerliponase alfa vs. SoC on the proportion of patients experiencing the progressive symptoms reported in Table 19 in the CS seemed clinically plausible. The clinical adviser considered, however, that the number of annual seizures in the CS (see Table 20) as opposed to proportion of patients experiencing seizures was difficult to interpret and comment on. He also noted that the annual number of seizures requiring rescue medication may have been underestimated for both cerliponase alfa and SoC for health states 7 to 9. However, the differences highlighted by the clinical adviser were modest and unlikely to impact the estimates of cost-effectiveness.

The EAG considers that the uncertainty on the magnitude of impact of cerliponase alfa on seizures can potentially impact on the estimates of cost-effectiveness, given the size of cost savings in seizure management for cerliponase alfa vs. SoC in the company's base-case analysis [redacted]. The EAG did not, however, conduct scenario analyses addressing this issue, due to lack of more appropriate data sources to explore this uncertainty.

#### 4.2.7.4 *Vision loss*

The company modelled the proportion of patients affected by vision loss in the same way for both treatment groups, i.e.:

i. Assuming that vision loss would affect all patients in health states 7-9;
ii. Furthermore, the proportion of patients with vision loss was assumed to increase linearly from 0% at age 6 to 100% at age 20 years old in health states 1-6.

The company assumed (i) to maintain alignment with the vignettes used to inform health state utilities (see Section 4.2.10), which described patients in health states 7-9 as functionally blind. Assumption (ii) was informed by clinical opinion.[31]

Vision loss is associated with a utility adjustment and costs (see sections 4.2.10 and 4.2.11.9, respectively).

***Points for critique***

Clinical advice to the EAG suggests that for the majority of patients with CLN2 vision loss starts around 5 years of age and on average patients completely lose their vision by the time they reach 10 years. Patients with atypical CLN2 have lower disease progression on vision and may only have

complete loss by the time they are 20 years old, but this is not how the disease manifests for the majority of patients. Therefore, the company's assumption of linear increase in the proportion of patients with vision loss between 6 and 20 years, may underestimate the disutility associated with vision loss for 'all patients' but particularly for patients treated with cerliponase alfa 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.

In the original HST12, the NICE committee's preference was to assume no impact of cerliponase on vision loss, and this was implemented in the model by assuming that the proportion of patients with vision loss is the same for individuals treated with cerliponase alfa in health states 1-6 as for those treated with the standard of care. The company approach in the current CS still implies some delay to vision loss compared to SoC, as in the company's base case analysis some patients in the SoC arm will reach health state 7 before they are 6 years old and will thus incur the costs of vision loss earlier (but not associated loss of HRQoL) earlier than those treated with cerliponase alfa. The EAG considers that the original HST12 approach to modelling vision loss is more appropriate than the CS, given that the clinical evidence submitted by the company did not suggest that cerliponase alfa improves or stabilises vision loss in the long-term as acknowledged by the company (see Section 3.4.2). The EAG, notes, however, that short-term clinical evidence presented in Section 3.3.3, suggests that vision may be preserved for a time, with little vision loss in the first three years of treatment. However, vison appears to be lost rapidly, thereafter.

The EAG explores alternative ways to model progressive vision loss in section 6.

**Issue: The company's approach to modelling progression of vision loss with age may not reflect the natural disease progression and favour the cost-effectiveness of cerliponase alfa.**

#### 4.2.7.5 *Mortality*

The company's model applied age and sex adjusted general population mortality (informed by England and Wales life tables for 2018/20)[41] to individuals in all 'alive' health states. As detailed in section 4.2.7.2, in the company's base-case analysis, disease specific mortality only applied to individuals in health state 9 and the risk of death was not modified by treatment with cerliponase alfa. The company justifies the exclusion of neuro-disability related mortality as due to no deaths being observed in cerliponase alfa trial programme in which neuro-disability was the cause.[11, 42]

The company excluded from their base-case analysis the mortality associated with adverse events from the economic model and assumed that mortality associated with infections from ICV treatment zero, because deaths had not been observed in study 190-201/202 (see Table 85, CS).

At the EAG's request, the company presented additional scenario analysis including:

i. Neuro-disability mortality risk modelled as per NICE's committee preference for HST12;
ii. Infection related infection-related mortality due to being bedbound.

Both scenarios had a modest impact on the estimates of cost-effectiveness.

***Points for critique***

The EAG main concern is the clinical plausibility of the life expectancy predictions of the economic model, particularly for patients treated with, cerliponase alfa. In the company's base case analysis, the undiscounted mean life years gained (LYG) in the model were approximately 54.0 and 6.0 years (with half-cycle correction) for cerliponase alfa and SoC, respectively. The model also predicts a median age of death for the company's base case of approximately 56.3 and 7.7 years (with half-cycle correction) for cerliponase alfa and SoC, respectively. The median age of death in studies on the natural history of the disease (i.e., for individuals untreated with cerliponase) was between 8.6-10.1 years old (Table 5, CS). The assumption that patients experience general population mortality in health states 1-8 does not seem unreasonable to the EAG, in the context of the standard care arm, where the primary cause of death is related to disease progression and the mean and median survival times, predicted by the model, do not exceed life expectancy of patients receiving standard care based on external data. In the CS (section B.2.12.1), the company states that the median age of death for the 190-201 matched controls to study 190-201/202 was 10.4 years. Corresponding values for the matched controls used to inform the SoC clinical parameters of the model are not reported in the CS, but this suggests that if anything the estimates of LYG for the SoC are pessimistic. For patients treated with cerliponase alfa the mortality assumptions may be overly optimistic. Furthermore, the considerable extension to life expectancy with cerliponase alfa compared to SoC predicted by the model (approximately 48 undiscounted LYG on average) is accrued largely beyond the observed follow-up on clinical trials (which does not seem to extend much beyond 6 years), and thus, affected by considerable uncertainty. By applying disease specific mortality only to individuals in health state 9, the cerliponase alfa treatment effect on disease progression translates into considerable life extension for patients treated with this technology. Therefore, the assumptions on stabilisation contribute largely to the life expectancy extension for the patients treated with cerliponase alfa. We note that if 'all patients' treated with cerliponase alfa are assumed to be non-stabilisers (and 100% enter the model in health state 2 at the age of 2 years old), the expected life years gained in the model are reduced to 27.2 years (with half-cycle correction).

The clinical advisor to the EAG considered that the life expectancy of patients treated with cerliponase alfa is highly uncertain and that company's base-case predictions for this outcome may be too optimistic. The clinical advisor also noted that from the moment patients become bed-bound their risk of mortality increases (in the model, this would correspond to health states 7 to 9), as lack of mobility increases the risk of potentially fatal infections. The company's additional mortality scenario

including health state dependent (neuro-disability) mortality do not address this concern, as they do not allow separating the combined impact of a high proportion of stabilisers and delays to progression for cerliponase alfa over the model time horizon on mortality. This is because patients in health state 1-2 are only exposed to 12% excess mortality over that of the general population and the model estimates that for cerliponase alfa patients remain in these two health states on average 17.6 years (discounted at 3.5% annual rate and half-cycle corrected).

Other HTAs have considered infections and neuro-disability related mortality in their models. [35][SMC, HST12] In the original HST12, the ERG also noted the need to explore the long-term effects of loss of ambulation and increasing neuro-disability, and this was accepted by the NICE committee in their preferred set of assumptions. The EAG considers that the evidence presented by the company is not sufficient due to its short-term nature to justify deviating from the NICE committee's preferred assumption of including neuro-disability related mortality in the original HST12.

**Issue: The company's base-case analysis may underestimate mortality for patients treated with cerliponase alfa, suggesting a considerable extension to life expectancy compared to the SoC which is not sufficiently supported by existing empirical evidence.**

### 4.2.8 Treatment discontinuation

The company's model assumes treatment with cerliponase alfa is discontinued once the individual enters health state 6 (ML score of 1; from this point, patients are assumed to receive SoC) or at death, if it occurs before reaching health state 6. The company states that it is anticipated that patients have progressed once they have achieved health status 6 that continued treatment with cerliponase alfa would be unlikely to improve motor and language function. Discontinuation at health state 7 is explored in a scenario analysis, where it results in a [redacted] increase to the company's base-case incremental ratio of cost-effectiveness (ICER) with the cerliponase alfa list price and an increase of [redacted] to the incremental cost of cerliponase alfa vs. SoC (see Table 97, PfCs response). Impact on incremental QALYs was, however, modest. The assumption of no treatment discontinuation was also tested in scenario analysis driving the ICER up by [redacted] (see Table 97, PfCs response).

Treatment with SoC was assumed to be continued throughout the time horizon.

***Points for critique***

The company's justification for the stopping rule applied for cerliponase alfa is inconsistent with the estimate transition probabilities for health states 6 and 7, as the transition probabilities from health state 6 to 5 and from 7 to 6 are greater than zero for individuals treated with cerliponase alfa and, thus backwards transitions from health state 6 and 7 to less severe health states are still possible (see Table

16). An important implication of this is that patients who transition back from health state 6 to 5, restart treatment with cerliponase alfa again (and once more accrue associated benefits and costs). This is unlikely to happen in clinical practice.

The company states that when patients discontinue treatment with cerliponase alfa, patients are assumed to switch to SoC transition probabilities. This is implemented in the model by switching the source of transition matrices when health state reaches health state 7 or greater from cerliponase alfa to that of SoC (as illustrated in the discontinuation adjusted transition matrix reproduced in Table 16 – probabilities highlighted in grey have been adjusted for discontinuation in the company's base-case analysis), so some treatment effect of cerliponase alfa remains. The EAG notes that patients treated with cerliponase alfa remain in health state 6 for 3.2 years on average, under the company's base case assumptions. The clinical adviser to the EAG suggested that while you might expect some treatment effect to remain between 6-9 months after cerliponase alfa discontinuation, you would not expect patients to remain for 3 years in these health state without treatment. In contrast the costs and utilities become the same as for SoC from the point of treatment discontinuation.

**Figure 14 Transition matrix adjusted for discontinuation for initial stabilisers (extracted from economic model)**

| Cerliponase alfa | | To state | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Death |
| From state | 1 | 99.75% | 0.25% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| | 2 | 2.91% | 94.40% | 2.69% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| | 3 | 0.00% | 0.45% | 96.25% | 3.29% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| | 4 | 0.00% | 0.00% | 3.58% | 93.23% | 3.19% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| | 5 | 0.00% | 0.00% | 0.00% | 0.57% | 98.39% | 1.04% | 0.00% | 0.00% | 0.00% | 0.00% |
| | 6 | 0.00% | 0.00% | 0.00% | 0.00% | 1.33% | 97.92% | 0.75% | 0.00% | 0.00% | 0.00% |
| | 7 | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 96.23% | 3.77% | 0.00% | 0.00% |
| | 8 | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 96.23% | 3.77% | 0.00% |
| | 9 | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 96.23% | 3.77% |
| | Death | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 100.00% |

The EAG discussed treatment stopping criteria in clinical practice with the clinical adviser. He considered that this would depend heavily on the family preferences. Some families might prefer to continue treatment while a benefit on quality of life was maintained (particularly due to seizure control), while other might consider treatment discontinuation as early as health state 5 (ML score 2) due to the perception that any benefits would be offset by the need to subject the child to regular infusions.

The stopping criteria for cerliponase alfa in the MAA and clinical studies differed. In the former, treatment discontinuation depends on a number of criteria including i) age at treatment initiation, ii) time on treatment, iii) decline in ML score that has persisted for 3 or more infusions, and iv) reduction in proxy reported patient quality of life (as measured by PedsQL, EQ-5D-5L and CLN2 quality of life assessment). Implementing this is not feasible with the current model structure. The large majority of patients in the clinical trial programme appear to have remained on treatment during the studies follow-up.

In the original HST12, treatment discontinuation was assumed to occur at health state 7. The company has not justified why they have chosen to deviate from the previous assumption on treatment discontinuation. The EAG considers that, given the lack of further evidence to strongly support discontinuation of cerliponase alfa at health state 6 and the issues highlighted above around the implementation of the discontinuation rule in the model, it remains more appropriate to assume that treatment discontinuation occurs at health state 7.

**Issue: The company's base-case assumption on treatment discontinuation is insufficiently justified by existing evidence and may disproportionally favour the cost-effectiveness of cerliponase alfa compared to SoC due to how the stopping rule was implemented in the economic model.**

### 4.2.9 Adverse events

The company included in the economic model the most common drug-related AEs reported in Study 190-202 for patients treated with cerliponase alfa, i.e., pyrexia, hypersensitivity, headache, and vomiting. No AEs were modelled for the SoC, as this was defined as established clinical management without cerliponase alfa. The model considered the proportion of patients experiencing each event (see Table 51, CS), which was assumed to apply at every model cycle and was sourced from Study 190-202.[39] AEs included in the model had associated disutility and costs (see section 4.2.10.2 and section 4.2.11.7, respectively).

At the clarification stage the company justified the exclusion of other alternative sources of safety data (namely studies 190-203, 190-501, 190-502 and 190-504) by stating that the use of AE data from Study 190-201/202 is expected to be conservative given the higher proportion of patients experiencing adverse events in the preferred evidence source compared to the alternatives. The company presents data to support this statement in Table 73 of the response to PfCs, where summary safety data is contrasted across studies. The EAG notes that the comparison does not, however, include the proportion of patients experiencing each AE included in the economic model across studies. The table also does not indicate the set of most common drug-related AEs in each study. The EAG requested at the clarification stage that a scenario analysis was conducted whereby ICV device related infections

were included, similarly the original HST12.[43] The company's scenario assumed a 0.125% of patients would have am ICV device related infection as informed by clinical opinion. This proportion is lower than previously assumed in the original HST12 (0.45%), but in line with clinical advice received by the company in a previous advisory board [redacted]. [32] The company also provided in response to PfCs scenario analyses exploring the impact on cost-effectiveness of i) doubling AE rates and ii) setting AE rates to zero. All additional scenario analyses had a small impact on the ICER of cerliponase alfa vs. SoC (see Table 74 and 78, response to PfCs), particularly the scenario including ICV device related infections.

***Points for critique***

Clinical advice to the EAG confirmed that, while events of device related infections were lower in clinical practice than on the cerliponase alfa clinical trial programme, patients treated with cerliponase alfa would still be at risk of these adverse events and this AE should be considered in the cost-effectiveness analysis. Therefore, the EAG considers that in principle this AE should not have been excluded from the company's base-case analysis, the impact of it is marginal as shown by the company's additional analyses.

Furthermore, the EAG is reassured by the company's additional scenario analyses that AEs are not a driver of cost-effectiveness for cerliponase alfa vs. SoC and, thus, no related issues warrant further exploration.

### 4.2.10 Health related quality of life

#### 4.2.10.1 *Systematic Literature Review*

The company undertook a systematic literature review (SLR) to identify studies reporting original HRQoL data on individuals with confirmed CLN2 or TTP1 deficiency. A description of the searches and some the search strategies were included in Appendix H of the CS. EAG's. Additional information on the SLR was provided in the company's response to the points for clarification (PfC), a further document was provided by the company, which included explanations for errors identified by the EAG.. The EAG reports an appraisal of the company's evidence identification approach in Table 46 Appendix 2.

This review was an update of the systematic literature review conducted to inform utilities in the original HST12. The original searches were performed in January 2017 and updated in January 2024. The company identified three published studies [44] [19] [1] and one cerliponase alfa for CLN2 SMC submission [35] that met the pre-defined inclusion criteria (see Table 8, Appendix H of the CS). The studies included in the SLR are summarised in Table 9 (Appendix H of the CS). These studies were not assessed for bias but their relevance to the NICE reference case was evaluated and reported in Table 12 in Appendix H of the CS. In all studies utilities were derived from EQ-5D-5L valued

directly [44] [1] or mapped to EQ-5D-3L. [1], [35], [19] The studies assessed the utilities of caregivers and siblings of patients with CLN2 [19], [44] and of patients using clinical experts as proxies. [35] Although the company did not detail in the CS how the identified studies were used to inform the economic model, the utility estimates elicited in one of the studies.[1] were applied in the company's base-case analysis.

The company considered that it was not clear whether the study by Ballinger et al. (2016) [44] was consistent with NICE reference case because of the tariff applied. The other three studies were assessed as not meeting the requirements of the reference case because the utility values were not derived from patients and/or carers but from clinical experts [35], [1] or family members [19] (see Table 12 in Appendix H of the CS).

***Points for critique***

The EAG notes that some studies [19] [44] identified by the company do not strictly comply with the inclusion and exclusion criteria defined by the SLR, as these specified a population of patients with confirmed CLN2 disease (any variant) or TPP1 deficiency. Two studies reported only caregivers and siblings (i.e., no self-report or proxy response for individuals with CLN2 disease). This suggests that the inclusion criteria were broader than what is described in Table 8 in Appendix H of the CS in terms of population considered eligible. Nevertheless, the EAG considers that caregivers and siblings utilities are of relevance for the current appraisal. The EAG notes that the study used to inform the company's base-case analysis[1] is one of the studies which the company assessed as not complying with the NICE reference case due to the use of clinical experts as proxy responders for the patients.

4.2.10.2 *Utility values used in the economic model*

The company's model incorporated i) treatment specific health state utility for individuals with CLN2, ii) health state and treatment specific disutilies for siblings and caregivers of these individuals, iii) age and sex adjusted utility values in accordance with general population utility values, iv) vision loss-related utility adjustments, and v) adverse event-related disutility. All utility values applied in the economic model are outlined in Table 60 in the CS.

*4.2.10.3 Health state utilities for individuals with CLN2*

Health state utility values are applied to time spent in health states in the model in order to calculate quality-adjusted life years (QALYs) that reflect the improvement in HRQoL associated with each treatment group under comparison. Health state-specific utilities for patients were conditional on treatment received.

The company assessed HRQoL data from studies 190-201/202 and 190-203 and the MAA data collection. HRQoL in these evidence sources was collected from patient proxies (parent/guardian) using two generic HRQoL instruments (PedsQL and EQ-5D-5L), and one disease-specific instrument

(CLN2-QL). The CLN2-QL data cannot be incorporated into the model, because its score is not preference based. Thus, the CS did not report utility estimates and to the best of the EAG's knowledge, there are no mapping algorithms that allow deriving utility values from CLN2-QL

The company did not include in the model utilities derived from Study 190-201/202 in the model. The exclusion of these data is attributed to the small number of observations on EQ-5D-5L and PedsQL, inability to derive utility values for some health states, and absence of data to inform the utilities of patients receiving SoC. The company did not state why utilities derived from Study 190-203 were not applied in the model, but it is likely that the same data limitation applies as for Study 190-201/202 given Study 190-203 had a smaller sample size.

The company used the following sources of data to inform patient's health state utilities:

- Base-case analysis: utilities elicited from 8 clinical expert proxy responders in a vignette-based study by Gissen et al. (2021). [1]
- Scenario analysis: utilities derived from data collected in the context of the MAA.

The utility values applied in the base-case analysis are reported in Table 52 (CS). These utilities were derived by asking clinical experts to complete EQ-5D-5L questionnaires as a proxy for CLN2 patients using 18 vignettes describing the HRQoL for each health state. The scenarios described in the vignettes were based on the most prevalent combinations of the motor and language domain scores defining ML scores and other progressive symptoms occurring in each health state, with the latter differing according to treatment received (cerliponase alfa or SoC). The company stated that the vignettes were validated by a clinical expert with experience of CLN2 disease and cerliponase alfa treatment. The vignette health state descriptions were the same as the vignette descriptions used in the original HST12. The resulting EQ-5D-5L scores were mapped to EQ-5D-3L values using the Hernández Alava et al., 2020, algorithm.[38] Since the mapping algorithm includes gender as a variable, the company derived gender-specific utility values for each treatment and health state. Treatment specific health state utilities were weighted according to the baseline gender distribution in the model (50% female, 50% male). The mapping algorithm also uses age as a variable, but the company does not state what was assumed for this covariate when deriving utility estimates.

For the company's MAA scenario analysis, which applied utilities derived from the MAA database, the EQ-5D-5L values (collected every 6 months) were mapped to EQ-5D-3L values using the Hernández Alava et al., 2020 algorithm.[38] Given that the sex of new treatment starters in the MAA was not reported, a 50% split between female and male was assumed and the mapping was performed

separately for these two groups. The company used the lowest age group reported in the Policy Research Unit in Economic Evaluation of Health and Care Interventions dataset (18-24 years) as a proxy for the overall MAA cohort. Furthermore, the company had to apply further assumptions to derive the SoC specific utilities as the MAA only included patients treated with cerliponase alfa. Furthermore, the MAA did not include patients in health states 8-9. Thus, in this scenario the company assumed the following:

- For patients treated with SoC:
    - The utility in health state 1 would correspond to the mean utility for those treated with cerliponase alfa in the same health state derived from the MAA data (i.e., 0.861 for women and 0.862 for men) minus the absolute difference between cerliponase alfa and SoC health utility in the base-case analysis (i.e., -0.012 for women and for men).
    - The utilities in health states 2-7 were estimated as the difference between health states within the same treatment arm. For example, the utility value for health state 2 in SoC arm was estimated as the utility value for MAA health state 1 in SoC arm (estimated as explained above) minus the difference between SoC health state 2 and SoC health state 1 in the study by Gissen et al. (2021).[1]
- For patients treated with SoC and cerliponase alfa in health states 8-9, the utility values were estimated as the utility value from the previous health state minus the difference between the health states within the SoC group in the study by Gissen et al. (2021). For example, the utility value for health state 8 in cerliponase alfa arm was estimated as the utility value for health state 7 in cerliponase alfa arm minus the difference between health state 8 and 7 in the same treatment arm.

The utility values used by the company in this scenario analysis are provided in Table 53 in the CS.

The company does not report the statistical model used to derive health states utilities for cerliponase alfa from the mapped EQ-5D-3L scores in the MAA scenario analyses. Thus, it is not clear how repeated utility measures in the MAA study were handled and if any within patient correlation was considered in their approach (e.g., by applying a linear mixed model).

***Points for critique***

The EAG is concerned about the quality of the study used to inform the health state utility values applied in the model, and the reliability of these elicited treatment specific utilities. First the EAG considers that there may be bias in the validation of vignettes given that it was performed by only one clinical expert who also participated in the Gissen et al. (2021) study.[1] Second, the vignettes described

different symptomatic burden between cerliponase alfa and SoC at the same health state, but it is not clear how the descriptive content of the vignettes is aligned with the assumed progressive symptoms burden in the economic model (see Section 4.2.7.3). Similar concerns were raised by the ERG in the original HST12, but the NICE committee concluded that treatment with cerliponase alfa could be associated with increased HRQoL beyond that achieved through delaying disease progressions and assessed the vignette study as the preferred assumption for health utilities. Third, the Gissen et al. (2021) study[1] uses clinical experts rather than carers as proxies which is a non-reference case method that may not accurately reflect patients' quality of life. However, the EAG noted in Section 4.2.10.1, that the main alternative source of evidence using family caregivers as proxies (i.e., MAA) may also be affected by bias. This is due to treatment continuation in the MAA being conditional in part to maintenance of a HRQoL benefit, which may have incentivised caregivers to report higher HRQoL than they would have otherwise.

The clinical adviser to the EAG confirmed that patients receiving cerliponase alfa experience fewer symptoms even if they have the same ML score compared to patients receiving SoC. Thus, the EAG considers this assumption as reasonable given the current structural assumptions. Yet, the EAG also notes an inconsistency in utility values between cerliponase alfa and SoC. The difference between cerliponase alfa and SoC is substantial for health states 5-9, with SoC having a utility value lower by 0.15 or more compared to cerliponase alfa. The clinical adviser stated that the difference between cerliponase alfa and SoC is predominantly driven by the higher number of seizures among patients receiving SoC, especially seizures that require rescue medication or hospitalisation. The EAG noted that the utility values dropped substantially for SoC in health state 5 compared to health state 4 while the number of seizures was assumed the same as in health state 4 (see Table 21). The clinical advisor confirmed that the drop in the utility values between these health states was expected and was due to a decline in mobility. However, the clinical expert indicated that the drop in mobility was expected among individuals receiving either of the treatments (cerliponase alfa or SoC). Thus, the utility values for cerliponase alfa were also expected to drop more substantially between health states 5 and 4, which was not the case. These inconsistencies in the utility values between cerliponase alfa and SoC indicate that applying treatment-dependent utility values may not correctly reflect the difference in HRQoL between individuals treated with cerliponase alfa and SoC. The EAG notes that a different structural approach could have been applied by the company, similarly to what was done to capture the resource use and costs of progressive symptoms (see section 4.2.11.8). This approach would model the impact of progressive symptoms other than those affecting the motor and language disease domains by assigning the symptom-related disutility to the proportion of patients experiencing these specific symptoms at each health state by treatment group. Although this approach was considered by the EAG as having the potential to better reflect the difference in HRQoL among individuals receiving cerliponase alfa and SoC, it was not performed by EAG as a scenario analysis because it

would require: i) substantial structural changes, ii) a further review of HRQoL to identify relevant disutility estimates for each symptom, and iii) an appropriate baseline utility that reflected the health state utility net of these progressive symptoms impacts.

**Table 21 Utility values applied in the base case and assumptions on the number of seizures per each health state (adapted from Table 46 and Table 52, CS).**

| Health state | Utility values | | Overall number of seizures | | Number of seizures that require rescue medication | |
|---|---|---|---|---|---|---|
| | Cerliponase alfa | SoC | Cerliponase alfa | SoC | Cerliponase alfa | SoC |
| 1 | 0.974 | 0.986 | 1 to 5 | 5 to 10 | 1 to 5 | 1 to 5 |
| 2 | 0.761 | 0.728 | 1 to 5 | >10 | 1 to 5 | 1 to 5 |
| 3 | 0.627 | 0.527 | 5 to 10 | >20 | 1 to 5 | 5 to 10 |
| 4 | 0.394 | 0.276 | 5 to 10 | >50 | 1 to 5 | 5 to 10 |
| 5 | 0.330 | 0.067 | 10 to 20 | >50 | 1 to 5 | 5 to 10 |
| 6 | 0.197 | 0.043 | >20 | >100 | 1 to 5 | 5 to 10 |
| 7 | -0.115 | -0.333 | >20 | >100 | 5 to 10 | >10 |
| 8 | -0.176 | -0.326 | >20 | >100 | 5 to 10 | >10 |
| 9 | -0.197 | -0.359 | >20 | >100 | >10 | >10 |

The company's scenario analysis applying utility values from the MAA utilised treatment-specific utility values even though the MAA provided utility values for cerliponase alfa only. As detailed above, the company estimated the utility difference between cerliponase alfa and SoC based on the vignettes and applied it to the MAA data. The EAG is concerned about the approach taken to derive utility estimates for the SoC. The company estimated the difference between cerliponase alfa and SoC for health state 1 and thereafter used the difference between health states in SoC arm. An alternative approach would have been to estimate MAA SoC health utilities by first estimating the utility difference between cerliponase alfa and SoC in the vignette study for each health state, and thereafter apply it to the cerliponase alfa MAA health state utilities to estimate SoC MAA.. The approach taken by the company leads to generally lower utility estimates for SoC than the alternative described by the EAG (see Table 22). Furthermore, estimating treatment-dependent utility values using MAA data leads to combining different sources (i.e., MAA data and estimates based on the vignette study), retains the issues regarding the robustness of Gissen et al., 2021, and further increases the uncertainty

associated with these parameters. The company's approach also makes limited use of comparative utility evidence between cerliponase alfa and the SoC in Gissen et al., 2021.[1]

**Table 22 Utility values used in the company's MAA scenario analysis and SoC MAA utility values used in the EAG's scenario analysis**

| Health state | Utility values used in the MAA scenario analysis in CS | | EAG's alternative utility values for SoC in the MAA scenario |
|---|---|---|---|
| | Cerliponase alfa | 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 |

Abbreviations: CS, company submission; EAG, external assessment group; MAA, managed access agreement; SoC, standard of care.

The company presented at the clarification stage, a conservative scenario analysis applying the utility values from the MAA to both treatment groups, which suggests a [redacted] increase of the ICER for cerliponase alfa vs. SoC (see Section 5.1.2). In contrast, applying the same assumption of treatment independent health state utilities informed by Gissen et al. 2021, the ICER rises by [redacted]. Both these scenario analyses, suggest that the treatment effect of cerliponase alfa on health state utilities is influential (if not a key driver of cost-effectiveness at the current drug price).

The EAG requested more details on the PedsQL data and a scenario analysis that applies EQ-5D-3L utilities derived from PedsQL™ data collected for patients in the 'all patients' pooled dataset. The company did not provide more detailed new information on the PedsQL data and did not conduct the requested scenario analysis. While the EAG does not consider that health state utilities should be applied in the base-case analysis, we note that the company presented analysis using PedsQL in their submission to the original HST12. Providing these data could have allowed a more comprehensive approach of how HRQoL evidence in patients treated with cerliponase alfa has developed since the previous appraisal and might help validate the magnitude of differences between consecutive health state utilities for this treatment group.

In light of all considerations, the EAG considers that while the Gissen et al., 2021, study is affected by considerable uncertainty, it remains the better evidence source for health state utilities.

**Issue: While the Gissen et al., 2021, study is the only study reporting comparative health state utilities for cerliponase alfa and the SoC, it is affected by considerable uncertainty and the**

**derived utility estimates may be affected by bias. The patient's health state utilities and magnitude of the cerliponase alfa treatment effect on health state utilities is an important area of uncertainty.**

**Issue: The company's scenario analysis incorporating health state utility evidence from the MAA, may have overestimated the magnitude of the cerliponase alfa treatment effect on health state utilities.**

*4.2.10.4 Disutility burden for caregivers and siblings*

Caregiver and sibling disutility estimates applied in the company's base case analysis are reported in Tables 57 and 58 of the CS, respectively. The company assumed a health state and treatment specific disutilities to reflect loss of HRQoL for caregivers and siblings of individuals with CLN2; disutilities applied during the first 30 years in the model time horizon.

The number of caregivers per patient by health state and the proportion of care that would be provided by family caregivers and non-family caregivers were informed by the 2016 Delphi panel conducted for the original HST12. [4] In this previous appraisal, the company compared the UK EQ-5D-5L crosswalk score with matched norms (age-group and gender) taken from Health Survey for England (2010) and found that UK caregivers had a significantly lower EQ-5D-5L score, with a difference of –0.108. To derive health state specific disutilities, the company assumed lower disutility values for health state 1 and 2 based on clinical opinion (-0.02 and -0.025 for health state 1 2, respectively). [30] For the remaining seven health states, disutility was assumed to increase linearly, with –0.108 being applied to the midpoint of these remaining seven health states. In addition to these assumptions, which were in line with the original HST12, the current CS incorporated an additional assumption on different impact of the disease on caregivers depending on the treatment provided. More specifically, during an advisory board meeting held in November 2023 to validate the caregiver disutilities, clinicians stated that patients treated with cerliponase alfa experience fewer progressive symptoms compared to patients treated with SoC within the same health state. Based on this statement, the company assumed that utility values differ between cerliponase alfa and SoC for caregivers, siblings and patients. The caregiver disutility for the cerliponase alfa treatment group was assumed to be 50% of the disutility assumed for those treated with the SoC.

Sibling disutility was applied across all but the first two health states based on clinical experts' opinion. [30] The value for sibling disutility of -0.09 was obtained from a report on the challenges of living with and caring for a child affected by CLN2 disease.[45] This disutility was assumed to increase linearly, with -0.09 applied to the midpoint of these remaining states (health state 6). It is assumed a patient has 0.94 siblings, based on a Batten Disease Family Association survey. These assumptions were in line with the original HST12. Similarly to the caregiver disutility assumptions in the CS,

sibling disutility for the cerliponase alfa treatment group was assumed to be 50% of the disutility assumed for those treated with the SoC.

***Points for critique***

The EAG considered it is reasonable to expect the disease to have an impact on the HRQoL of children's family members and caregivers over and above what is captured by movement across health states. However, the EAG is concerned about the assumed magnitude of cerliponase alfa treatment effect on caregiver and sibling, which appears to be arbitrary. Thus, the EAG explores uncertainty in this parameter further in Section 6.

**Issue: The magnitude of the cerliponase alfa treatment effect on caregiver and sibling disutility is an area of uncertainty, which the company has not fully explored.**

*4.2.10.5 Vision loss related utility adjustment*

Given that progressive vision loss is expected to happen in early disease stages and the vignettes do not capture it in health states 1-6, the company applied a utility multiplier to all patients in health states 1–6 as follows: 1 for those aged <6 years, 0.87 for those aged >20 years, and a linear decline between 1 and 0.87 for patients between 6 and 20 years. The value of 0.87 reflects the QoL in patients with neovascular macular degeneration in the UK .[46]

***Points for critique***

The EAG reiterates here concerns about the company's approach not reflecting the disease progression impact on vision (see section 4.2.7.4), as cerliponase alfa is not expected to impact on progressive vision loss compared to SoC. The use of the 0.87 vision loss multiplier is, however, in line with the estimate preferred by the NICE committee preference for the original HST12 even if its implementation of vision loss progression in the model is not in line with the previous appraisal.

*4.2.10.6 General population utility adjustment*

The company's model included general population multipliers applied to the utility values. No information was provided in the CS about these multipliers and their sources. In the response to PfCs, the company indicated that the general population utility values were taken from Hernández-Alava et al., 2020, [38] in line with current NICE guidance. Health state utility values from Gissen et al .,2021,[1] were applied at the start of the model and for every subsequent year, a multiplier was applied based on the ratio between the general population utility values for current and starting age in the model.

***Points for critique***

Given the additional explanation provided in the company's response to the points for clarification letter, the EAG has no concerns about the applied general population multiplier.

#### *4.2.10.7 Adverse events*

Section 4.2.9 details the AEs considered in the economic model. Table 54 of the CS summarises the evidence used to derive annual disutility estimates assumed for each included AE, and which are the same values as used in the original HST12 (with the exception of ICV device related infections – see section 4.2.9). ICV device related infections were, however, considered in a scenario analysis submitted by the company at PfCs (Table 78, PfCs response); the disutility assumed for this AE was informed as per the original HST12.

***Points for critique***

The scenario analyses presented at the clarification stage reassured the EAG that the modelling of HRQoL loss due to cerliponase alfa is not an issue of concern for the cost-effectiveness analysis.

### 4.2.11 Resources and costs

#### *4.2.11.1 Confidential pricing arrangements*

The EAG notes that there are no confidential commercial arrangements in place for drugs comprising the comparator regimen or subsequent treatments. While the cost-effectiveness analyses in the CS incorporate a confidential pricing arrangement this had not yet received the required approval by NHS England and, thus, cannot be considered in the EAR. The treatment acquisition costs used in the analyses presented in EAR (Sections 5 and 6) consider the costs of cerliponase alfa at its publicly available list price. At NICE's request, the EAG presents corresponding analyses to those in Sections 5 and 6 including a patient access scheme (PAS) price for cerliponase alfa consisting of a simple discount of [redacted] over its list price, which had also not been approved by NHS England at the time the EAG's analyses were conducted and is, therefore, considered provisional.

#### *4.2.11.2 Resource use and cost evidence in the published literature*

The methods and results of the SLR conducted as part of the appraisal for the identification of relevant cost and health care resource use data are presented in Appendix I of the CS. The company's searches were an update (conducted in January 2024) of the company's corresponding SLR conducted for the original HST12 (searches conducted in January 2017). The company considered eight publications [47] [19, 34, 35] [44] [48] [49] [50] suitable for inclusion; these are summarised in Table 9 in Appendix I of the CS. These publications consisted of six surveys and two HTA submissions. The company does not explicitly state if the identified studies informed resource uses and costs in the CS.

***Points for critique***

The overall SLR was mostly clear and comprehensive, with several exceptions detailed in Table 47 in Appendix 2. Overall, the EAG is not concerned that relevant studies have not been identified by company, but notes that Williams et al., 2017, study [40] used to inform CS in the original HST12 and

current appraisal, was not identified via the company's updated searches. Furthermore, none of the studies identified by the company's SLR appear to have been used to inform the cost-effectiveness analysis. Given the description of the studies in Table 9 in Appendix I of the CS, this seems appropriate.

*4.2.11.3 Resource use and costs applied in the model*

The company's economic model includes costs related to i) cerliponase alfa acquisition and administration, ii) monitoring and clinical management of patients by health state, iii) AEs, iv) progressive symptoms (including epilepsy maintenance treatment), v) vision loss, and vi) residential care. These are summarised and critiqued in this section alongside other categories of cost not originally included in the company's economic model (i.e., costs associated with psychiatric/behavioural support, diagnostic testing of CLN2 disease). Unit costs are mostly informed by national published sources, such as NHS reference costs, [51] the Personal Social Services Research Unit (PSSRU) costs, [52] the British National Formulary (BNF) [53] and the Drugs and pharmaceutical electronic market information tool (eMIT) [54], inflated to 2021/22 prices where appropriate and discounted at an annual rate of 3.5%. Annual costs (unless otherwise stated) in the company's base-case analysis are summarised by category in Table 23.

**Table 23: Summary of costs included in the company's base-case analysis**

| Item | Model input | EAR Section |
|---|---|---|
| **Annual drug acquisition costs** | | |
| **Cerliponase alfa** | £524,577.27* | Section 4.2.11.4 |
| **SoC** | £0 | |
| **Annual drug administration costs** | | |
| **Cerliponase alfa** | One-off insertion cost: £13,871<br>Replacement costs: £956<br>Infusion costs: £22,831 | Section 4.2.11.5 |
| **SoC** | £0 | |
| **Annual health state costs** | | |
| **Cerliponase alfa** | HS 1: first year £5,478 subsequent years £8,407<br>HS 2: first year £5,478 subsequent years £8,407<br>HS 3: first year £7,678 subsequent years £10,607<br>HS 4: first year £18,740 subsequent years £25,372<br>HS 5: first year £20,662 subsequent years £27,295<br>HS 6: first year £29,784 subsequent years £36,255<br>HS 7: first year £33,870 subsequent years £36,806<br>HS 8: first year £34,054 subsequent years £36,989<br>HS 9: first year £35,630 subsequent years £38,565 | Section 4.2.11.6 |
| **SoC** | HS 1: first year £5,269 subsequent years £8,079<br>HS 2: first year £5,269 subsequent years £8,079<br>HS 3: first year £7,469 subsequent years £10,279<br>HS 4: first year £18,531 subsequent years £25,044<br>HS 5: first year £20,454 subsequent years £26,967<br>HS 6: first year £29,453 subsequent years £35,966 | |

| | | |
|---|---|---|
| | HS 7: first year £33,540 subsequent years £36,517<br>HS 8: first year £26,471 subsequent years £29,449<br>HS 9: first year £28,047 subsequent years £31,025 | |
| **Annual adverse event costs** | | |
| **Cerliponase alfa** | £936.68 | Section 4.2.11.7 |
| **SoC** | £0 | |
| **Annual progressive symptom costs** | | |
| **Cerliponase alfa** | HS1 £1,350.52<br>HS2 £1,363.51<br>HS3 £1,411.86<br>HS4 £1,454.40<br>HS5 £1,620.68<br>HS6 £2,042.50<br>HS7 £4,884.31<br>HS8 £4,902.26<br>HS9 £8,948.43 | Section 4.2.11.8 |
| **SoC** | HS1 £1,373.80<br>HS2 £1,475.99<br>HS3 £4,480.01<br>HS4 £4,650.32<br>HS5 £4,875.34<br>HS6 £4,884.31<br>HS7 £8,939.46<br>HS8 £8,948.43<br>HS9 £8,948.43 | |
| **Annual vision loss costs** | | |
| **Cerliponase alfa** | £4,561.74 | Section 4.2.11.9 |
| **SoC** | | |
| **Annual residential care costs** | | |
| **Cerliponase alfa** | £49,359 | Section 4.2.11.10 |
| **SoC** | | |

*assumes patients are at least 2 years old. Abbreviations: HS, health state; SoC, standard of care.

#### *4.2.11.4 Drug acquisition costs*

The list price of cerliponase alfa is £20,107 per 300 mg pack, consisting of two 150 mg vials. In line with the SmPC, the drug dose and number of vials of cerliponase alfa required per infusion is modelled according to age (see Table 61, CS).

Additionally, an adherence rate of 97.0% for cerliponase alfa, derived from the overall cohort in the MAA, was applied to adjust the cost. The evidence used to inform the acquisition costs for cerliponase alfa in the company's base-case is summarised in Table 62 of the CS. The SoC is assumed to not have associated acquisition costs, as this was defined as established clinical management without cerliponase alfa (i.e., not an incremental cost).

***Points for critique***

The adherence rate used in the model (97%) was collected in MAA and not from the company's preferred base-case clinical evidence source (i.e., Study 190-203, dosing compliance [redacted] over the entire dosing period) [11] to inform the baseline health state distribution and transition probabilities for health states 1-7. The EAG notes, however, that the adherence rate suggested by Study 190-203 is very close to the observed rate in the MAA. The EAG considers that, while the parameterisation of the adherence in the base-case analysis is not consistent with the effectiveness parameterisation, this is not an issue for the cost-effectiveness analysis given the similarity of the alternative estimates and that the EAG does not consider Study 190-203 to be the most appropriate source to inform the clinical effectiveness of cerliponase alfa. Ideally, the EAG would have preferred to use the adherence rate in the 'all patients' dataset but acknowledges this is likely to be close to 97%.

#### *4.2.11.5 Administration costs*

The administration costs associated with cerliponase alfa include those associated with implanting the ICV device (one-off cost of the initial surgical implantation of the device and replacement every 4 years, in line with cerliponase alfa's SmPC).[3] delivery the infusion by a trained healthcare professional knowledgeable in ICV administration. Furthermore, it was assumed that the cost of the ICV would happen every 4 years in line with the recommendations of the SmPC. The evidence used to inform the infusion costs for cerliponase alfa in the company's base-case is summarised in Table 63 and 65 of the CS. Similarly to acquisition costs, the SoC is assumed to not have associated administration costs.

***Points for critique***

The EAG is concerned that the costs of ECG monitoring during infusion was not included in the model, as per the NICE committee preference in the original HST12; this exclusion was not justified in the CS. In the previous appraisal, the cost of an ECG was applied to all patients on treatment every six months and to the proportion of patients with heart disorders (patients with present or past bradycardia, conduction disorders, or with structural heart disease) requiring an ECG every infusion, as recommended in the technology's SmPC. The EAG considers that the omission of this cost is, thus, not appropriate and explores this issue further in Section 6.

The EAG notes that it is unclear whether the costs of replacing the ICV device have been under or overestimated by the company. The EAG further notes that the frequency of replacement assumed in the company's model is aligned with the recommendations of cerliponase alfa's SmPC.[3]

In the model, the company did not include the costs associated with acquiring the ICV device, and it indicated that these costs are typically covered by the institution where the device implantation is performed. EAG considers that the cost to the health care system should have been considered, thus increasing the total costs associated with the new technology. However clinical advice to the EAG

suggests that this cost should be marginal and, therefore, this is not expected to have an impact on the cost effectiveness results.

**Issue: The company's exclusion of the costs associated with ECG monitoring of patients during infusion of cerliponase alfa is not in line with the drug's SmPC and the NICE committee preferences in the original HST12. This exclusion was not justified and is likely to underestimate the cost of administering cerliponase alfa.**

*4.2.11.6 Health state costs*

The cost of visits to healthcare professionals was considered by health state with frequencies of some health care contacts differing between cerliponase alfa and SoC patients. Unit costs were taken from the NHS reference costs 2021/22 or the PSSRU[55] [52]. Detailed unit costs references are shown in Table 67 of the CS.

Annual health state resource use frequencies were derived from clinical expert opinion during the Delphi panel. [30] Health state resource use was further validated in an advisory board, held with clinical experts, in November 2023. [32] It was considered in the advisory board the following resource use should not be included for SoC patients: i) ophthalmologist appointments (any health state), and ii) critical care bed days for patients in health states 8 and 9. Furthermore, a clinical expert advised that for patients receiving treatment with cerliponase alfa, an average of one annual cardiologist appointment per year should be applied in all states. Thus, these elements were updated in the company's model. With the exception of the resource use categories described above, all other resource use frequencies are estimated the same for both cerliponase alfa and SoC patients in corresponding health states as per the original HST12. Resource use estimates are presented for cerliponase alfa and SoC patients in Tables 65 and 66 of the CS, and costs per health state and treatment group are reported in Table 23.

***Points for critique***

The EAG considers the company's approach to be appropriate.

*4.2.11.7 Adverse events costs*

Section 4.2.9 details the AEs considered in the economic model; unit costs for these AEs were derived from NHS reference costs 2021/22 (see Table 68, CS).[55]

***Points for critique***

As highlighted in Section 4.2.9, the company did not include ICV device related infections in the base-case. The clinical advisor to the EAG described the clinical management of AE as consisting of antibiotic treatment for up to 2 weeks and, if infection had not been controlled by then, replacement of the ICV device. However, he also noted that he was not aware of any cases requiring ICV device

replacement in clinical practice. The company's scenario analysis including ICV device related infections costed the clinical management of this AE as a weighted average of the cost of alternative antibiotic regimens (see Tables 76-77, response to PfCs). The EAG notes that the majority of antibiotic regimens were assumed to be administered for a very short number of days (1-2 days), suggesting the cost of managing this AE may have been underestimated. Nevertheless, the EAG considers that this is unlikely to impact on estimates of cost-effectiveness for cerliponase alfa compared to the SoC, due to the low infection rate.

*4.2.11.8 Progressive symptoms and epilepsy costs*

Progressive symptoms included in the model have been previously described in section 4.2.7.3. Costs of progressive symptoms were derived by applying unit costs (mostly derived from the BNF) [53], eMIT [56] and NHS reference costs [55]) to the estimates of resource use reported in section 4.2.7.3 (Table 19 and Table 20) A summary of costs associated with the treatment of progressive symptoms overall by health state and treatment group are reported in Table 24.

**Table 24: A summary of costs associated with the treatment of progressive symptoms overall by health state and treatment group (adapted from the model, CS)**

| Health State | Cerliponase alfa Annual total costs (£) | SoC Annual total costs (£) |
|---|---|---|
| 1 | £1,350.52 | £1,373.80 |
| 2 | £1,363.51 | £1,475.99 |
| 3 | £1,411.86 | £4,480.01 |
| 4 | £1,454.40 | £4,650.32 |
| 5 | £1,620.68 | £4,875.34 |
| 6 | £2,042.50 | £4,884.31 |
| 7 | £4,884.31 | £8,939.46 |
| 8 | £4,902.26 | £8,948.43 |
| 9 | £8,948.43 | £8,948.43 |

Abbreviations: SoC, standard of care.

The average annual cost of anti-epileptic drugs (AEDs) was informed by medication usage in the trial. It was assumed that all patients would receive treatment with AEDs, based on the patient narratives from the 190-201 and 190-202 studies where all patients in the trial received some form of AEDs. [42]

Medications required for the treatment of distress, dystonia and myoclonus were informed by Williams et al., 2017. [40] For the treatment of each of these progressive symptoms, it was assumed that all medications were equally likely to be used, as there were no data to inform this parameter from the cerliponase alfa trials. Some of the treatments for myoclonus and dystonia are also prescribed for the

treatment of epilepsy, so to avoid double counting of medications the company did not apply these costs to the progressive symptoms (only to AEDs).

***Points for critique***

As mentioned in Section 4.2.7.3, the EAG main concern is the lack of connection when modelling the impact of progressive symptoms on HRQoL and costs. The vignettes used in Gissen et al., 2021 [1] (the study used to inform health state utilities - see section 4.2.10.2) describes progressive symptoms for each health state and treatment group, that do not align with the level of resource elicited to inform costs of progressive symptoms. Firstly, the number of annual seizures described in the vignette study is aligned with the resource use for these parameters applied in the original used in HST 12, which as illustrated in Table 20 assumes considerably fewer seizures than those in the company's current model. Furthermore, in health states 7 to 9, the vignettes described that patients do not experience generalised tonic-clonic seizures regardless of treatment group, while in the company model it is assumed that annual seizures requiring medication differs between treatment in health states 7 and 8 and the annual number of these seizures is higher in health states 7 to 9 compared to the remaining 'alive' health states. Secondly, in the vignettes feeding tubes are assumed to be required from health state 2 onward for SoC and from health state 4 onwards for cerliponase alfa treatment group. However, in the company's model, the proportion of patients requiring a feeding tube in the cerliponase alfa treatment group is 0% in health states 1-4 and only 20% of these patients require a feeding tube in health state 5 (see Table 19). Finally, the vignettes included spasticity, which was not explicitly included as a progressive symptom in terms of resource use.

The EAG received clinical advice suggesting that fewer than 5% cerliponase alfa patients need hospitalisation (for approximately one week) and 40-50% SoC patients need hospitalisation (for approximately two to three weeks) with patients in both treatment groups requiring rescue medication. The model does not account for different compositions of treatment for seizures according to treatment group, which might suggest that the cost per seizure requiring medication for patients treated with cerliponase alfa may have been underestimated. However, given the other uncertainties highlighted in Section 4.2.7.3 around validating the differential resource use by treatment group and health state, the EAG considers that attempting to better characterise seizure management by treatment group according to clinical opinion is unlikely to make the estimates of cost-effectiveness more robust.

The EAG considers that, while it is reasonable to assume a treatment effect for cerliponase alfa on the resource use of progressive symptoms at each health state. However, the magnitude of this treatment effect is uncertain. The EAG considers that the uncertainty on the magnitude of impact of cerliponase alfa on seizures can potentially impact on the estimates of cost-effectiveness, given the size of cost savings in seizure management for cerliponase alfa vs. SoC in the company's base-case analysis

[redacted]. The EAG did not, however, conduct scenario analyses addressing this issue, due to lack of more appropriate data sources to explore this uncertainty.

The EAG notes that the magnitude of treatment effect on progressive symptoms other than seizures is also a concern to the EAG, because it was not modelled in the original HST12 (only differences in seizures were considered between treatment groups). The EAG further explores the uncertainty on the within health state impact of cerliponase alfa compared to SoC on progressive symptoms other than seizures, in Section 6.

**Issue: The magnitude of the cerliponase alfa treatment effect on resource use associated with progressive symptoms is an area of uncertainty, which the company has not fully explored.**

*4.2.11.9 Vision loss costs*

The company applied the costs associated with vision loss to i) all patients in health states 7-9 and ii) a proportion of patients in health states 1-6, which rose linearly from 0 at age 6 to 100% at age 20. This was applied equally to both treatment arms. The unit cost for vision loss were calculated as per the original HST12 and are reported in Table 80 of the CS.

***Points for critique***

The calculation of the costs associated with vision loss matches the NICE committee's preferred approach in the original HST12. However, as for the disutility associated with vision loss the implementation in the model, does not fully align with the NICE committee's preferences in the original HST12 (see section 4.2.7.4).

*4.2.11.10 Residential care costs*

The company considered that a proportion of patients would require residential care once they became adults. The company sourced the proportion of patients entering residential care for each health state from the published literature.[57]Since this source was not specific to CLN2 patients and reported estimates by severity of learning disabilities, the company assumed the following correspondence between ML scores and the severity of learning disabilities:

- ML 6 and 5 - no learning disabilities
- ML 4 and 3 - mild/moderate learning disabilities
- ML 2 and 1 - severe learning disabilities
- ML 0 - profound multiple learning disabilities.

The assumed proportion of patients requiring residential care per health state is reported in Table 83, CS. The annual cost of residential is £49,359 which was estimated from Unit Costs of Health & Social Care 2016 [58] and inflated to 2021-22 prices using PSSRU 2022.[52]

***Points for critique***

The EAG notes that the proportion of adult patients requiring residential care in the original HST12 was 50% regardless of health states. The company's approach in the current appraisal, implies a potential treatment benefit for cerliponase alfa on this category of costs resulting from delays to progression. However, the EAG notes that in one of the company's advisory boards, clinical advisors considered [redacted].[32] This suggests uncertainty on the level of resource use associated with residential care needs for adult patients. However, the EAG considers it unlikely that this uncertainty will impact on the estimates of cost-effectiveness and, therefore, does not explore this issue further.

*4.2.11.11 Diagnostic testing costs*

The company did not originally include diagnostic testing costs in the model as all patients with CLN2 disease are expected to get diagnosis. The NICE scope specifies that the costs associated with diagnostic testing for CLN2 in people with CLN2 disease who would not otherwise have been tested should be included in the company's base-case analysis and a scenario analysis without this cost should also be presented. At the clarification stage, the company provided a scenario including the cost for enzyme activity testing of the TPP1 protein.

In the scenario analysis, the company assumed a cost per test of £100 and that 0.6% of patients tested would be eligible for treatment with cerliponase alfa, as informed by clinical opinion (see Table 89, response to PfCs). Thus, the total cost of testing was estimated to be £17,500 per patient treated with cerliponase alfa.

***Points for critique***

Clinical advice to the EAG suggests that testing is currently done for CLN2 disease because active treatment is available (i.e., cerliponase alfa). Thus, the EAG agrees that it is appropriate to exclude the cost of testing for CLN2 from the base-case analysis. The company's scenario analysis varying this assumption suggests a marginal impact on the estimates of cost-effectiveness (see section **5.1.2**). Therefore, EAG does not consider the exclusion of diagnostic test costs to be an issue likely to affect the estimates of cost-effectiveness.

*4.2.11.12 Psychiatric/behavioural support costs*

The company did not include the cost associated with providing psychiatric/behavioural support to patients over the age of 13 with a ML score over 1 (i.e. in health states 1 to 5), as per NICE committee's preferences in the original HST12. The company justified the exclusion as driven by clinical opinion received at one of the company's advisory boards.[32]

***Points for critique***

The clinical adviser to the EAG considered that the costs of psychiatric/behavioural should still be included in the cost-effectiveness analysis given the impact that CLN2 disease has on behavioural symptoms. The EAG further explores this issue in Section 6.

**Issue: The company's exclusion of the costs associated with psychiatric/behavioural support for patients in health states 1-5 differs from the NICE committee preferences in the original HST12. The company justified this exclusion based on clinical opinion, but clinical advice to the EAG suggests these costs should be included.**

# 5 COST EFFECTIVENESS RESULTS

## *5.1 Company's cost effectiveness results*

All cost-effectiveness results presented in this section incorporate the company's list price for cerliponase alfa. The EAG replicates the company's deterministic base-case at the provisional PAS price (see Section 4.2.11.1) in Appendix 4.

The cost-effectiveness results presented by the company and summarised in Section 5 suggest that the company's ICERs for cerliponase alfa are all above the maximum cost-effectiveness threshold used to inform NICE decision making in the context of highly specialised technologies (i.e., £300,000 per additional QALY).[59]

### 5.1.1 Company's base-case analysis

The results of the company's base-case analysis are presented in Table 25.

**Table 25 Base-case results cerliponase alfa vs SoC (adapted from Tables 93 and 95, response to PfCs)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | CE threshold (£/QALY)* |
|---|---|---|---|---|---|---|
| **Deterministic analysis** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Probabilistic analysis** | | | | | | |
| SoC | [redacted] | -0.14 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.50 | [redacted] | 17.64 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.
Abbreviations: CE, cost-effectiveness, ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

The company's base-case deterministic analysis suggests that compared to SoC, the cerliponase alfa is costlier by [redacted] and more effective resulting in 17.35 incremental QALYs, yielding an ICER of [redacted] per additional QALYs. The ICER of cerliponase alfa vs. SoC is, thus, considerably above the applicable cost-effectiveness threshold (i.e., £300,000 per additional QALY, as the undiscounted QALY gain for cerliponase alfa [redacted] implies a weight of 3 applies to the £100,000 cost-effectiveness threshold in the HST process.[43]. The probabilistic ICER for cerliponase alfa vs. SoC is approximately [redacted] higher than the corresponding deterministic estimate.

Disaggregated deterministic costs and QALYs are reported by the company in Table 98 of the response to PfCs and Table 2 of appendix J, respectively. The incremental costs of cerliponase alfa

compared to SoC are predominantly driven by the higher drug acquisition costs of cerliponase alfa ([redacted]% of the incremental costs of cerliponase alfa vs. SoC). Results also suggest that there are some cost savings with cerliponase alfa compared to SoC, driven by reductions in the costs associated with the management of progressive symptoms, particularly of seizures requiring rescue medication ([redacted] compared to SoC). The QALY gain with cerliponase alfa compared to SoC is mostly accrued in health state 1 (14.86 QALYs, 86%), as this is the health state where individuals in this treatment group spend more time over the model time horizon (35.29 vs. 0.72 undiscounted life-years gained [LYG]).

### 5.1.2 Company's sensitivity analyses

The company conducted the following sensitivity analysis: PSA, univariate deterministic sensitivity analysis (DSA) and scenario analyses. The company did not conduct subgroup analyses.

The PSA was run for 1,000 simulations; probability distributions used to obtain random drawers of most parameters in the model are reported in Table 84 (CS). For the model parameters varied in the PSA, empirically estimated measures of variance used to inform the simulation if available; where not available, standard errors were derived assuming a 20% variation around the mean value and applied. Probabilistic results are presented in Table 25.

. Further results informed by the PSA are presented on the cost-effectiveness plane (Figure 43, response to PfCs) and a cost-effectiveness acceptability curve (CEAC) is also presented (Figure 44, response to PfCs). The results suggest that cerliponase alfa is more likely to be cost-effective than the SoC at thresholds above approximately £700,000 per additional QALY.

The company's DSA was conducted by varying most model inputs using 95% confidence intervals where possible, or ±20% of the mean value. The company presents in Table 96 (response to PfCs) and in a tornado diagram (Figure 45, response to PfCs) results for the ten most influential model inputs. The DSA suggests that cost-effectiveness results are most sensitive to variation in the transition intensities (and therefore, the transition probabilities) of cerliponase alfa (particularly for transitions from health 1 to 2 and from 5 to 6) and the vision loss utility multiplier.

The company's conducted scenario analysis to explore the impact of varying structural assumptions, as described in Table 90, CS). In addition to the 11 scenarios reported in the CS, the company conducted further scenarios analyses, at the request of the EAG. Results for the full set of the company's scenario analyses are shown in Table 26.

**Table 26: Scenario analysis results for cerliponase alfa (adapted from Tables 97, PfC response)**

| | Incremental costs | Incremental QALYs | ICER (£/QALY) | % change from base-case ICER |
|---|---|---|---|---|
| **Base case** | [redacted] | 17.35 | [redacted] | [redacted] |
| Treatment discontinuation at health state 7 (ML score 0) | [redacted] | 17.79 | [redacted] | [redacted] |
| No treatment discontinuation | [redacted] | 17.86 | [redacted] | [redacted] |
| Starting distribution: Study 190-203 | [redacted] | 11.78 | [redacted] | [redacted] |
| Starting distribution: MAA (new patients) | [redacted] | 7.82 | [redacted] | [redacted] |
| Source of transitions: All patients | [redacted] | 14.27 | [redacted] | [redacted] |
| Source of transitions: All patients (piecewise at 6 months) | [redacted] | 22.86 | [redacted] | [redacted] |
| Duration of ML 6 stabilisation: 12 years | [redacted] | 18.52 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 75% | [redacted] | 19.54 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 100% | [redacted] | 22.11 | [redacted] | [redacted] |
| Source of utility values: MAA | [redacted] | 16.88 | [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: Gissen 2021, treatment-independent utility values | [redacted] | 16.88 | [redacted] | [redacted] |
| Scenario: MAA (all patients), treatment-independent utility values | [redacted] | 15.03 | [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: CE, cost-effectiveness, ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care

The assumption applied for the baseline distribution of individuals across health states at model entrance is the most impactful on the ICER of cerliponase alfa vs. SoC. This is particularly the case when patients are assumed to enter the model in the health states they were on at the start of treatment in the MAA new starter cohort ([redacted] of the ICER), with only 18.2% patients starting in health state 1 while the majority of patients, 45.5% started treatment in health state 3. This means that, compared to the base-case analysis, considerably fewer patients are initial stabilisers under this assumption and therefore, fewer patients will remain in health state 1 for first 6 years and then progress at a slower rate in the model compared to non-stabilisers. It is also worth noting that

alternative baseline distributions have a considerable impact on the (undiscounted) incremental QALYs of cerliponase alfa vs. SoC, implying a cost-effectiveness threshold lower than £300,000 per additional QALY (£139,886 and £235,792 per additional QALY when assuming the MAA new starters cohort and Study 190-203 baseline distributions, respectively).

Another scenario analysis with considerable impact on both the ICER for cerliponase alfa vs. SoC ([redacted]) and the cost-effectiveness threshold implied by the QALY gains (£246,232 per additional QALY), is the scenario where transition probabilities for health states 1-7 are informed by the 'all patient' dataset.

Scenario analyses which appear to considerably increase the ICER for cerliponase alfa vs. SoC (but do not impact the applicable cost-effectiveness threshold) include those with alternative treatment discontinuation rules, as well as those applying health states utilities are assumed treatment independent and/or health state utilities were sourced from the MAA. In contrast, the ICER for cerliponase alfa vs. SoC seems to reduce by [redacted], when the piecewise model is used to inform the transition probabilities for health states 1-7.

The company's cost-effectiveness sensitivity analyses (PSA, DSA and scenario analyses) results all suggest that the ICER for cerliponase alfa vs. SoC lies above £300,000 per additional QALY.

## *5.2 Model validation and face validity check*

### 5.2.1 Company's validation of the economic model

The model underwent internal validation by the model developers and one health economist who had not been involved in the model development. The company does not detail what this internal validation entailed. The key modelling assumptions and inputs were validated in a series of advisory boards, which included two clinical experts with experience in the treatment of CLN2. and technical and clinical validation of the model (see Section B.3.14, CS). The company did not conduct external validation of the model and justifies this by stating that CLN2 disease is rare and there is lack of available treatments.

The company also performed, at the EAG's request at the clarification stage, a comparison between observed clinical outcomes and model outputs. The clinical effectiveness outcomes assessed to demonstrate the clinical effectiveness of cerliponase alfa compared to SoC (e.g., time to unreversed 2-point decline in ML score or score of zero and rate of decline in ML score) are not the same used to inform the economic model (see section 3.3). This hinders assessing the internal validity of the model predictions vis-à-vis the observed data. The EAG requested at PfCs a comparison of observed and

economic model predicted ML score decline rates at different time points, which is presented (Table 91 in response to PfCs).

The company caveated that the ML score rate of decline from the trials assumes perfectly linear decline, and does not account for the impact of death (i.e., that patients with the lowest ML scores are expected to die sooner, increasing the average ML score in those who are alive); the latter is particularly relevant in the natural history data who are expected to die earlier. Furthermore, predicted model estimates for the 'all patients' dataset assume a starting age and distribution from the full population in Study 190-203, and transitions from the pooled 'all patients' data, and assumes no stabilisation. While this means that a direct comparison is not straightforward, the EAG notes that the company could have increased comparability by aligning the age and ML score distribution in the model for the 'all patients' analysis with the observed patients' characteristics for this population. In addition to the points raised by the company in response to PfCs, it is apparent that:

- In the 'all patients' matched dataset, the predicted ML score decline rate becomes lower than the corresponding trial rate for cerliponase alfa at 288 weeks (approximately 5.4 years), and at 192 weeks (approximately 3.7 years) for the SoC.
- In the Study 190-203 matched dataset, the predicted ML score decline rate becomes lower than the corresponding trial rate at 144 weeks (approximately 2.8 years) for the SoC, but never is lower than observed for cerliponase alfa over the observed follow-up (although the gap between predicted and observed decline rates is getting smaller.

The EAG is concerned that this may indicate that the economic model predictions for cerliponase alfa for the majority of the time horizon may be too optimistic when compared to the observed 'all patients' data. Although the same inflection is seen earlier for the SoC (and in both datasets), the EAG notes that patients treated with SoC arrive to the death state much quicker than those treated with cerliponase alfa, and thus, the proportion of the time horizon with more optimistic than observed decline rates should not have as large an impact as for cerliponase alfa.

### 5.2.2 EAG's validation of the model

The EAG validated the company's model by conducting face-validity checks, detailed examination of formulas, and reproducing the results of the company's analyses. No programming errors were identified.

# 6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

All cost-effectiveness results presented in this section incorporate the company's list price for cerliponase alfa. The EAG presents all corresponding deterministic analyses to those in this section at the provisional PAS price (see Section 4.2.11.1) in Appendix 4.

## *6.1 Exploratory and sensitivity analyses undertaken by the EAG*

A summary of the issues identified and critiqued in section 4, along with the scenario where the EAG addresses each issue in its additional analyses is shown in Table 27.

**Table 27 Summary of the issues identified by the EAG.**

| Critique item from section 4 and description<br>The EAG considers: | | Explored in scenario | In EAG's base case | Area of remaining uncertainty | Significant impact on ICER | Section EAR |
|---|---|---|---|---|---|---|
| **Model structure** | | | | | | |
| Issue | The impact of the link between disease progression in terms of motor and language symptoms and progression in other disease symptoms, as well as the treatment effect of cerliponase alfa on the latter symptoms, are uncertain and difficult to validate, based on the evidence presented by the company. Furthermore, the treatment effect of cerliponase alfa on progressive symptoms is modelled in an inconsistent way between costs and HRQoL impacts. | No | NA | Yes | Unknown | 4.2.3 |
| **Population** | | | | | | |
| Issue | The baseline distribution of patients in the model is a key cost-effectiveness driver and area of uncertainty. Company's preferred distribution may be overly skewed towards higher ML scores given current and future clinical practice, according to clinical advice received by the EAG. | 1 | Yes | Yes | Yes | 4.2.4 |
| **Treatment effectiveness – initial stabilisation** | | | | | | |
| Issue | Initial stabilisation assumption for patients treated with cerliponase alfa is highly uncertain despite the additional evidence generated since original HST12 and more conservative assumptions have not been explored. | 2, 3 | Partly | Yes | No, but impacts on cost-effectiveness threshold | 4.2.7.1 |
| **Treatment effectiveness – transition probabilities health states 1-7** | | | | | | |
| Issue | The company's preferred evidence source to inform the transition probabilities in health states 1 to 7 for patients treated with cerliponase alfa, Study 190-203, may not reflect the | No, but in company's scenario analyses | Yes | Yes | Yes | 4.2.7.1 |

| Critique item from section 4 and description<br>The EAG considers: | | Explored in scenario | In EAG's base case | Area of remaining uncertainty | Significant impact on ICER | Section EAR |
|---|---|---|---|---|---|---|
| | population in current and near future clinical practice and be overestimate treatment effectiveness of the technology. Furthermore, Study 190-203 has a smaller sample size and fewer number of events to inform transition probabilities than the 'all patient' dataset. | | | | | |
| Issue | Comparative effectiveness was established based on a fairly naïve matched comparison in the absence of direct evidence, which is a source of uncertainty and insufficiently characterised by the company in order to comment on the likely direction of bias. | No | NA | Yes | Unknown | 4.2.7.1 |
| Issue | The EAG cannot establish whether the statistic model applied to estimate the transition probabilities for health states 1-7 provides robust estimates for the transition probabilities applied in the model, due to the unclear impact of using arbitrary initial values to inform the MSM models and the potential overfitting of these models to the observed data. Furthermore, the company did not test alternative estimation methods for these transition probabilities, which contributes to the uncertainty around the robustness of these parameters. | 4 | No | Yes | No, but impacts on cost-effectiveness threshold | 4.2.7.1 |
| **Treatment effectiveness – Vision loss** | | | | | | |
| Issue | The company's approach to modelling progression of vision loss with age may not reflect the natural disease progression and favour the cost-effectiveness of cerliponase alfa. | 5 | Yes | Yes | Yes | 4.2.7.4 |
| **Treatment effectiveness - Mortality** | | | | | | |
| Issue | The company's base-case analysis may underestimate mortality for patients treated with cerliponase alfa, suggesting a considerable extension to life expectancy compared to the SoC which is not sufficiently supported by existing empirical evidence. | 6 | No | No | No | 4.2.7.5 |
| **Treatment discontinuation** | | | | | | |
| Issue | The company's base-case assumption on treatment discontinuation is insufficiently justified by existing evidence and may disproportionally favour the cost-effectiveness of cerliponase alfa compared to SoC due | No, but in company's scenario analyses | NA | Yes | Yes | 4.2.8 |

| Critique item from section 4 and description<br>The EAG considers: | | Explored in scenario | In EAG's base case | Area of remaining uncertainty | Significant impact on ICER | Section EAR |
|---|---|---|---|---|---|---|
| | to how the stopping rule was implemented in the economic model. | | | | | |
| **Health related quality of life** | | | | | | |
| Issue | While the Gissen et al., 2021, study[1] is the only study reporting comparative health state utilities for cerliponase alfa and the SoC, it is affected by considerable uncertainty and the derived utility estimates may be affected by bias. The patient's health state utilities and magnitude of the cerliponase alfa treatment effect on health state utilities is an important area of uncertainty. | No, but in company's scenario analyses | NA | Yes | Unknown | 4.2.10.2 |
| Issue | The company's scenario analysis incorporating health state utility evidence from the MAA, may have overestimated the magnitude of the cerliponase alfa treatment effect on health state utilities. | 7 | No | Yes | Yes | 4.2.10.2 |
| Issue | The magnitude of the cerliponase alfa treatment effect on caregiver and sibling disutility is an area of uncertainty, which the company has not fully explored. | 8 | No | Yes | No | 4.2.10.2 |
| **Resources and costs - Treatment administration** | | | | | | |
| Issue | The company's exclusion of the costs associated with ECG monitoring of patients during infusion of cerliponase alfa is not in line with the drug's SmPC and the NICE committee preferences in the original HST12. This exclusion was not justified and is likely to underestimate the cost of administering cerliponase alfa. | 9 | Yes | Yes | Yes | 4.2.11.5 |
| **Resources and costs – progressive symptoms** | | | | | | |
| Issue | The magnitude of the cerliponase alfa treatment effect on resource use associated with progressive symptoms is an area of uncertainty, which the company has not fully explored. | 10 | No | Yes | No | 4.2.11.8 |
| **Resources and costs – psychiatric/behavioural support** | | | | | | |
| Issue | The company's exclusion of the costs associated with psychiatric/behavioural support for patients in health states 1-5 the NICE committee preferences in the original HST12. The company justified this exclusion based on clinical opinion, but clinical advice to the EAG suggests these costs should be included. | 11 | Yes | No | No | 4.2.11.12 |

Abbreviations: CE, cost-effectiveness, ECG, electrocardiogram, EQ-5D, EuroQol- 5 Dimension; ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; ML, motor function and language; NICE, national institute for health and care excellence; QALYs, quality-adjusted life years; SoC, standard of care; SmPC, Summary of Product Characteristic.

### 6.1.1 Developing the EAG base case

The scenario analyses which the EAG considered in defining our base case are described below and summarised in Table 28.

**Table 28 Building the EAG base case - description of implemented scenarios.**

| Scenarios | Description |
|---|---|
| 1. Baseline characteristics | Alternative distributions of patients across health states at model entrance and corresponding starting ages, according to:<br>• Clinical opinion on current clinical practice<br>• Clinical opinion on clinical practice in 5-year time<br>• Original HST12 |
| 2. Stabilisation assumption – proportion of initial stabilisers | Proportion of initial stabilisers assumed to be 80% of those in health state 1 at baseline, as per clinical advice to the EAG. |
| 3. Stabilisation assumption – reduction in transition probabilities after initial stabilisation | Transitions beyond 6 years for initial stabilisers occur at:<br>• The same rate as non-stabilisers (100% progression multiplier) applied to estimate the transition probabilities of stabilisers<br>• 75% the rate of non-stabilisers (75% progression multiplier) applied to estimate the transition probabilities of stabilisers |
| 4. Backwards transitions to healthier states not allowed | Transition probabilities for patients in health state 1-7 treated with cerliponase alfa are constrained so that transitions to a previous healthier state are not possible. |
| 5. Vision loss | Vision loss is modelled:<br>• Assuming the proportion of patients with vision loss increases linearly from 0% to 100% between the ages of 6 to 10 years old for both treatments.<br>• Assuming that the proportion of patients with vision loss for cerliponase alfa is not lower than the cumulative proportion of patients who progress to vision loss in the SoC, as per the original HST 12. |
| 6. Neuro-disability mortality for health states 6-9 | The neuro-disability mortality relative risks from the original HST12 only apply to health states 6-9 (ML score 0), as per clinical opinion. |
| 7. Alternative treatment effect of cerliponase alfa on health state utilities | In this scenario, the EAG estimated health state utilities for SoC when using MAA EQ-5D estimates for cerliponase alfa by applying the same difference in utilities between treatments at each health state as in Gissen et al., 2021.[1] |
| 8. Impact of cerliponase alfa on caregivers and siblings disutilities | The caregivers and siblings disutilities applied to cerliponase alfa at each health state is assumed to be:<br>• The same as for the SoC disutilities<br>• 75% of the SoC disutilities |
| 9. Including ECG monitoring costs | Inclusion of ECG monitoring costs every 6 months for all patients on treatment with cerliponase alfa and at every infusion for those patients with previously detected clinically significant ECG-12 abnormalities, as per original HST12 |
| 10. No impact of cerliponase alfa on progressive symptoms other than seizures | Assumes that the proportion of patients with progressive symptoms other than seizures is the same in both treatment group as elicited by the company's clinical experts for those treated with:<br>• Cerliponase alfa<br>• SoC |
| 11. Including psychiatric/ behavioural support costs | Inclusion of ECG psychiatric/ behavioural support costs for patients in both treatment groups aged 13 years and older, as per original HST12 |

#### *6.1.1.1 Scenario 1: Baseline characteristics*

In Section 4.2.4, the EAG highlighted concerns that that the company's preferred baseline distribution of patients across the health states at model entrance may be overly skewed towards higher ML scores, given current and expected future clinical practice within the next 5 years. In this scenario

analysis, the EAG explores alternative distributions informed by clinical advice to the EAG (scenarios 1.1 and 1.2) and by the NICE committee's preferences in the original HST (scenario 1.3). These distributions are summarised alongside the assumed starting age in the model in Table 29.

**Table 29: Baseline distribution across health states and age scores at model entrance**

| Scenario | HS 1 | HS 2 | HS 3 | HS 4 | HS 5 | HS 6 | HS 7 | HS 8 | HS 9 | Age (years) |
|---|---|---|---|---|---|---|---|---|---|---|
| Company base-case | 87.5% | 12.5% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 2 |
| 1.1. Clinical opinion – current practice | 15% | 45% | 30% | 10% | 0% | 0% | 0% | 0% | 0% | 4.5 |
| 1.2. Clinical opinion – in 5-year time | 50% | 35% | 12.5% | 2.5% | 0% | 0% | 0% | 0% | 0% | 3.5 |
| 1.3. Original HST12* | 50% | 50% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 4 |

*Assumptions and evidence sources used to inform decision making
Abbreviations: HS, health state; HST, highly specialised technology.

The EAG notes that the starting age in scenario 1.3 does not correspond to the starting age in the original HST12. In the previous appraisal, this parameter was informed by Study 190-201/202 matched to Study 190-901 (4.8 years). The EAG assumed that the starting age in Scenario 1.3 was 4 years, because that is the midpoint between the starting ages suggested by clinical opinion for the corresponding patient distribution. The clinical adviser to the EAG considered that the age at diagnosis/treatment initiation is likely to be 3.5 and 4.5 years for patients at health state 1 and 2, respectively.

#### *6.1.1.2 Scenarios 2 and 3: Stabilisation assumptions*

The EAG discussed in section 4.2.7.1, that the initial stabilisation assumptions for patients treated cerliponase alfa is highly uncertain and that the company did not explore a set of more conservative assumptions. In these scenario analyses, the EAG explores the impact on cost-effectiveness estimates of assuming:

- Scenario 2: that the proportion of initial stabilisers corresponds to 80% of those in health state 1 at baseline, as per clinical advice to the EAG. The company preferred assumption was that all patients in health state 1 at baseline are initial stabilisers and remain in this health state for the first 6 years in the model unless they die first.
- Scenario 3: more conservative transition probabilities in health states 1-7 for initial stabilisers beyond the initial 6 years in the model, which in the company's base-case were assumed to correspond to half of the non-stabilisers transition probabilities into/from health states. In scenario 3.1 the EAG assumes the same rate of progression as for non-stabilisers (100%

progression multiplier) applied to estimate the transition probabilities of initial stabilisers. In scenario 3.2 the EAG assumes 75% of the non-stabilisers rate of progression (25% progression reduction) applied to estimate the transition probabilities of initial stabilisers.

#### *6.1.1.3 Scenario 4: Backwards transitions to healthier states not allowed*

The EAG expressed in section 4.2.7.1, concerns about the estimation of transition probabilities in health states 1-7. The EAG is particularly concerned about the uncertainty surrounding the transition probabilities estimated using the MSM R package. More specifically, the EAG is concerned about the unclear impact of using arbitrary initial values to inform the MSM models and the potential overfitting of these models to the observed data. The company did not provide sufficient data to allow exploring alternative estimation methods (including different statistical methods and different levels of aggregation of health state transitions). Furthermore, the EAG noted in Section 4.2.7.1, that concerns as to whether backward transitions (i.e., transitions to a healthier health state) reflect sustained improvements to the condition or just temporary improvements that are not expected to persist. As noted in Section 4.2.7.1, by allowing for these backward transitions, some patients treated with cerliponase alfa can transition to increasingly healthier health states over the time horizon, which may not be clinically plausible. This scenario is a blunt tool to explore how the EAG's concerns about the robustness of the transition probability estimates may impact on the estimates of cost-effectiveness.

Thus, the EAG explores in scenario 4 the impact of applying a restriction to the cerliponase alfa transition probabilities for patients in health state 1-7 so that transitions to previous healthier states are not possible. In this scenario, the EAG assumed that the probability of remaining in each health state for cerliponase alfa would increase by the same value as the probability of transitioning to the adjacent healthier state in the company's base case analysis.

#### *6.1.1.4 Scenario 5: Vision loss*

The EAG noted, in Section 4.2.7.4, that the company's approach to modelling progression of vision loss with age may not reflect the natural disease progression and favour the cost-effectiveness of cerliponase alfa. In scenario 5 the EAG explores the impact of modelling progression vision loss by assuming:

- Scenario 5.1: That the proportion of patients with vision loss increases linearly from 0% to 100% between the ages of 6 to 10 years old for both treatments (instead of between 6 and 20 years as assumed in the company's base-case). This scenario was informed by clinical advice to the EAG.

- Scenario 5.2: That the proportion of patients with vision loss for cerliponase alfa is not lower than the cumulative proportion of patients who progress to vision loss in the SoC, as per the original HST12.

#### *6.1.1.5 Scenario 6: Neuro-disability mortality for health states 7-9*

The EAG identified in Section 4.2.7.5 that the company's base-case analysis may underestimate mortality for patients treated with cerliponase alfa, suggesting a considerable extension to life expectancy compared to the SoC which is not sufficiently supported by existing empirical evidence. While the company included at PfCs a scenario where the neuro-disability associated mortality was incorporated for health states 1 to 9 as per the NICE committee's preference in the original HST, clinical advice received by the EAG suggested that the relative risks for neuro-disability related mortality applied in the original HST12 might only apply to health states 7-9 (ML score 0). Thus, the EAG modelled this alternative assumption in Scenario 6.

#### *6.1.1.6 Scenario 7: Alternative treatment effect of cerliponase alfa on health state utilities*

In Section 4.2.10.2., the EAG noted concerns that the company's preferred evidence source to inform the heath state utilities of patients with CLN2[1] might not accurately reflect the impact of cerliponase alfa compared to SoC on these parameters. The EAG also noted that using the EQ-5D collected in the MAA presented a few limitations, one of which was that it still required using data from the Gissen et al., 2021,[1] and therefore, did not allow mitigating the concerns raised for that evidence source and further increased the uncertainty associated with these parameters by combining different sources (i.e., MAA data and estimates based on the vignette study). The EAG also noted that the company's scenario using the EQ-5D collected in the MAA as an alternative source of evidence, estimated the health state utilities for SoC by assuming the same utility difference between adjacent health states for SoC in Gissen et al., 2021.[1] The EAG noted in Section 4.2.10.2 that this may leads to generally lower utility estimates for SoC than estimating MAA SoC health state utilities by applying the utility difference between cerliponase alfa and SoC in Gissen et al., 2021., for each health state to the cerliponase alfa MAA health state utilities. Despite the limitations, the EAG notes that the latter approach, makes more use of comparative utility evidence between cerliponase alfa and the SoC in Gissen et al., 2021., than the one used by the company. Since the treatment effect of cerliponase alfa on health state utilities is an area of uncertainty, the EAG explored in scenario 7 the use of alternative estimates for the SoC utilities when using MAA data for cerliponase alfa (see values applied in this scenario in Table 22).

#### *6.1.1.7 Scenario 8: Impact of cerliponase alfa on care and siblings disutilities*

As highlighted in Section 4.2.10.2., the magnitude of the cerliponase alfa treatment effect on caregiver and sibling disutility is an area of uncertainty, which the company has not fully explored. The company assumed in their base-case analysis that sibling disutility for the cerliponase alfa treatment

group was 50% of the disutility assumed for those treated with the SoC. The EAG explores two alternative (more conservative) assumptions whereby the caregivers and siblings disutilities applied to cerliponase alfa at each health state is assumed to be:

- Scenario 8.1: The same as for the SoC disutilities
- Scenario 8.2: 75% of the SoC disutilities

#### *6.1.1.8 Scenario 9: Including ECG costs*

In section 4.2.11.5, the EAG noted that the company's exclusion of the costs associated with ECG monitoring of patients during infusion of cerliponase alfa is not in line with the drug's SmPC and the NICE committee preferences in the original HST12. In scenario 9, the EAG includes the additional the costs of ECG monitoring (unit cost £672, currency code: EY51Z, electrocardiogram monitoring or stress testing, day case, NHS reference costs 2020/21)[55] to the infusion costs of cerliponase alfa. It was assumed that all patients on treatment with cerliponase alfa received ECG monitoring every six months, and to the proportion of patients with heart disorders requiring ECG monitoring at every infusion. The proportion of patients requiring an ECG with each infusion was estimated from the MAA cohort (see Table 9), where 3% of patients had clinically significant ECG-12 abnormalities at baseline, rising to 27% at 3.5 years (42 weeks). The EAG notes that the information reported in the CS, does not allow identifying the proportion of patients who have had at least one prior ECG clinically significant result and furthermore, not all patients had a 42 weeks follow-up. Therefore, the estimated proportions of patients who require ECG monitoring at every infusion is an approximation. For comparison, in the original HST12, the ECG considered that these proportions where 10% at baseline and 71% at 2 years, based on evidence from the Study 190-201/202. The EAG considers that this scenario is likely to underestimate the proportions of patients who require ECG monitoring at every infusion.

#### 6.1.1.9 *Scenario 10: No impact of cerliponase alfa on progressive symptoms other than seizures*

The company assumed a treatment effect of cerliponase alfa on the resource associated with progressive symptoms at each health state, as detailed in Section 4.2.11.8. The EAG is concerned about the robustness of the implied cerliponase alfa treatment effect, particularly from progressive symptoms other than seizures. In the absence of primary data that allows validating the elicited estimates preferred by the company, the EAG explores the potential impact of these treatment effect on the estimates of cost-effectiveness by conducting the following extreme (conservative) scenarios, where it assumed that the proportion of patients with progressive symptoms other than seizures is the same in both treatment group as elicited by the company's clinical experts for those treated with:

- Scenario 10.1: Cerliponase alfa
- Scenario 10.2: SoC

*6.1.1.10 Scenario 11: Including psychiatric/ behavioural support costs*

Clinical advice to the EAG suggests that it is appropriate to include in the model the costs associated with psychiatric/behavioural support for patients (older than 13 years) in health states 1-5 the NICE committee preferences in the original HST12 (see Section 4.2.11.12). Therefore, in scenario 11, the EAG applied to both treatment groups the cost of psychiatric/behavioural support patients over the age of 13 with a ML score over 1 (i.e. in health states 1 to 5). In line with the original HST12 unit costs were sourced from NHS reference costs (unit cost £329, Child and Adolescent Mental Health Services - Community contacts, NHS reference costs 2020/21)[55] (NHS Reference Costs,) and applied every quarter in the model.

## *6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

All results for the EAG's scenarios are based on a deterministic analysis because it was not feasible to run the model probabilistically across all scenarios within the time constraints of the HST. The scenario analyses results presented in Table 30 to Table 40 refer to the total and incremental costs, total and incremental QALYs, and ICERs; all incremental estimates refer to cerliponase alfa vs. SoC. Given that the cost-effectiveness threshold of relevance is conditional on undiscounted QALY gains for cerliponase alfa vs. SoC, the tables also report the cost-effectiveness threshold as indicated by the incremental QALYs. For completeness and to add to the interpretation of the results, each table presents at its top the results of the company's base case analysis or the relevant company's scenario analysis.

Similarly, to the company's cost-effectiveness analyses results, the ICERs for cerliponase alfa vs. SoC are all above the cost-effectiveness threshold suggested by the undiscounted QALY gains for cerliponase alfa vs. SoC in each analysis. ICERs for cerliponase alfa vs. SoC in the EAG's scenario analyses range between [redacted] to [redacted]; these ICERs are higher than the company's base case ICER [redacted] in all but one scenario (Scenario 6 – Neuro-disability mortality included for health states 6-9). The applicable cost-effectiveness threshold ranges between £156,189 and £300,000 per additional QALY in the EAG's scenario analyses.

While the ICERs remain consistently above the cost-effectiveness threshold across scenarios, the following alternative assumptions particularly increase the ICERs:

1. <u>The baseline distribution of patients across health states (Scenario 1)</u>
   When the proportion of patients entering the model at healthier states, particularly those in health state 1, shifts to less healthy states, total costs and total QALYs decrease for both treatments, but more substantially for cerliponase alfa. The ICERs for these scenarios range between [redacted] (Scenario 1.1– clinical opinion of baseline distribution currently in the

NHS) and [redacted] per additional QALY (Scenario 1.3– baseline distribution as per the original HST12). This impact is largely driven by the reduction of individuals in health state 1 in these scenarios (compared to the company's base-case) to whom the initial stabilisation assumption for cerliponase alfa, which prevents progression for the first 6 years in the model and slows progression compared to non-stabilisers beyond that time point, applies. Compared to the company's base-case, the scenario with the most conservative assumption on the baseline distribution (Scenario 1.1.) reduces the undiscounted total life years (LYs) over the time horizon and in health state 1, from 53.99 LYs to 28.02 LYs, and from 35.29 LYs to 12.79 LYs. For less conservative scenarios (1.2. – clinical opinion of baseline distribution in 5-year time; and 1.3.), the total undiscounted LYs and over the time horizon and in health state 1, range from 40.89 LYs to 42.19 LYs and from 24.04 LYs to 25.28 LYs for scenarios 1.2 and 1.3 respectively. This suggests a considerable life extension with cerliponase alfa and time spent in the healthiest state (health state 1 with a ML score of 6) across all of these scenarios, even if these scenarios are all conservative compared to the company's base-case. Since these scenarios also have a large impact on incremental QALYs for cerliponase alfa vs. SoC compared to the company's base-case, the applicable cost-effectiveness thresholds for each of these scenarios are considerably lower than £300,000 per additional QALY. The applicable cost-effectiveness threshold ranges between £156,189 (Scenario 1.1.) and £271,234 per additional QALY (Scenario 1.3).

2. Vision loss (Scenario 5)
   The ICERs for cerliponase alfa vs. SOC increases to [redacted] per additional QALY in scenario 5.1 (vision linear decline with age between 6 and 10 years) and 5.2 (vision loss as per original HST12), respectively. In both scenarios, cerliponase alfa becomes more costly and less effective compared to what was suggested by the company's base-case, as in these analyses complete vision loss is assumed to occur earlier for patients treated with cerliponase alfa than under the company's preferred assumption.
3. Alternative treatment effect of cerliponase alfa on health state utilities (Scenario 7)
   In this scenario, which is a variation over the company's scenario using MAA to inform the utilities for cerliponase alfa, the ICER for cerliponase alfa vs. SoC is [redacted]. This is a substantial increase compared to the ICERs in the company's base-case analysis and their scenario using MAA utilities ([redacted]). This scenarios show that assuming the same treatment effect of cerliponase alfa vs. SoC on health state utilities as in Gissen et al., 2021, [1] to derive SoC utilities when using MAA evidence for cerliponase alfa suggests substantially lower QALY gains for cerliponase alfa vs. SoC compared to the company's scenario (15.51 vs. 16.20 QALYs). This further illustrates the uncertainty introduced by combining MAA and Gissen et al., 2021, utilities in

the absence of comparative evidence on health state utilities in the MAA, as it requires further judgements and assumptions. However, the EAG notes that the health state utilities are a potential driver of cost-effectiveness.

The following assumptions have considerable impact on reducing the applicable cost-effectiveness threshold (but a more modest impact on the ICERs), because they substantially reduce the incremental QALY gains for cerliponase alfa vs. SoC but also incremental costs (due to less time accruing the costs associated with cerliponase alfa:

1. Transition probabilities after 6 years for initial stabilisers closer to those of non-stabilisers (Scenario 3)
2. Backward transitions to healthier states not allowed for both treatment groups (Scenario 4)

The EAG notes that scenario 2, where only 80% of patients in health state 1 at baseline are assumed to be initial stabilisers (for the cerliponase alfa treatment group) is not as influential as scenario 1, despite also reducing the proportion of initial stabilisers. However, in this scenario 2 the proportion of the overall cerliponase alfa model cohort who are initial stabilisers (80% × 87.5% = 70%) is still considerably higher than in any of the alternative baseline distributions tested in Scenario 1.

ICERs are relatively insensitive to assumptions that increase the costs of cerliponase alfa compared to SoC, even if the impact on incremental costs is substantial. This is due to the considerably high total and incremental costs of cerliponase alfa even in the company's base case analysis ([redacted]). The EAG notes that the cost increase ([redacted]) due to introducing ECG monitoring costs for cerliponase alfa (Scenario 9) only increases the ICER by [redacted].

*6.2.1.1 Scenario 1: Baseline characteristics*

Table 30 presents the cost-effectiveness results of scenario 1, where alternative baseline distributions across health states and starting age in the model to those of the company's base case are tested. The alternative assumptions were informed by i) clinical advice (scenarios 1.1 and 1.2) to the EAG and ii) NICE committee's preferred assumptions for the original HST12 (scenario 1.3).

**Table 30 Cost-effectiveness results for scenario 1: Baseline characteristics**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: As per Study 190-203, < 3 years (HS1: 87.5%, HS2: 12.5%; age 2 years)** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 1.1: Current clinical practice (HS1: 15%, HS2: 45%, HS3: 30%, HS4:10%; age 4.5 years)** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| SoC | [redacted] | -1.10 | | | | |
| Cerliponase alfa | [redacted] | 7.77 | [redacted] | 8.86 | [redacted] | £156,189 |
| **Scenario 1.2: Clinical practice in 5-year time HS1: 50%, HS2: 35%, HS3: 12.5%, HS4:2.5%; age 3.5 years)** | | | | | | |
| SoC | [redacted] | -0.67 | | | | |
| Cerliponase alfa | [redacted] | 12.56 | [redacted] | 13.23 | [redacted] | £260,474 |
| **Scenario 1.3: As per original HST12 (HS1:50%, HS2: 50%; age 4 years)** | | | | | | |
| SoC | [redacted] | -0.59 | | | | |
| Cerliponase alfa | [redacted] | 13.25 | [redacted] | 13.84 | [redacted] | £271,374 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.
Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.2 Scenario 2: Stabilisation assumption – proportion of initial stabilisers*

Table 31 presents the cost-effectiveness results of scenario 2, where the proportion of initial stabilisers for cerliponase alfa is assumed to be 80% of those patients in health state 1 at model entrance (rather than 100% as in the company's base-case analysis), as informed by clinical advice provided to the EAG.

**Table 31 Cost-effectiveness results for scenario 2: Stabilisation assumption - proportion of initial stabilisers**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: 100% of patients in HS1 at model entrance are initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 2: –80% of patients in HS1 at model entrance are initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.02 | [redacted] | 16.30 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.
Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.3 Scenario 3: Stabilisation assumption – reduction in transition probabilities after initial stabilisation*

Table 32 presents the cost-effectiveness results of scenario 3, where the progression multiplier which is applied to derive the transition probabilities in health state 7-9 after 6 years in the model of initial

stabilisers is varied. Progression multipliers higher than 50% suggest that the transition probabilities in health state 1-7 after 6 years for initial stabilisers are closer in value to those of non-stabilisers when compared to the company's base-case analysis.

**Table 32 Cost-effectiveness results for scenario 3: Stabilisation assumption - reduction in transition probabilities after initial stabilisation**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: 50% progression multiplier for initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 3.1: 100% progression multiplier for initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 14.05 | [redacted] | 14.34 | [redacted] | £249,379 |
| **Scenario 3.2: 75% progression multiplier for initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 15.37 | [redacted] | 15.66 | [redacted] | £295,302 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.4 Scenario 4: Backwards transitions to healthier states not allowed*

Table 33 presents the cost-effectiveness results of scenario 4, where backwards transitions to healthier states not allowed for both treatment groups. This differs from the company's base-case analysis where backward transitions were allowed in health states 1-7 for cerliponase alfa. In this scenario, the EAG assumed that the probability of remaining in each health state for cerliponase alfa would increase by the same value as the probability of transitioning to the adjacent healthier state in the company's base case analysis.

**Table 33 Cost-effectiveness results for scenario 4: Backwards transitions to healthier states not allowed**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Backward transitions to healthier states allowed for cerliponase alfa only (HS 1-7)** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 4: Backwards transitions to healthier states not allowed** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 12.09 | [redacted] | 12.38 | [redacted] | £194,039 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.5 Scenario 5: Vision loss*

Table 34 presents the cost-effectiveness results of scenario 5, where the EAG varies the assumptions on the proportion of patients with vision loss over time according to i) clinical advice to the EAG (scenario 5.1) and ii) and NICE committee's preferred assumptions for the original HST12 (scenario 5.2).

**Table 34 Cost-effectiveness results for scenario 5: Vision loss**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Linear decline with age between 6 and 20 years old** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 5.1: Linear decline with age between 6 and 10 years old** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.57 | [redacted] | 16.85 | [redacted] | £300,000 |
| **Scenario 5.2: as per original HST12 (driven by cumulative proportion of vision loss in the SoC)** | | | | | | |
| SoC | [redacted] | -0.26 | | | | |
| Cerliponase alfa | [redacted] | 16.20 | [redacted] | 16.45 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.6 Scenario 6: Neuro-disability mortality included for health states 6-9*

Table 35 presents the cost-effectiveness results of scenario 6, where the EAG applied neuro-disability related mortality to individuals in health state 6 and 9 according to clinical advice to the EAG.

**Table 35 Cost-effectiveness results for scenario 6: Neuro-disability mortality included for health states 6-9**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Neuro-disability mortality excluded** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 6: Neuro-disability mortality included for HS6-9** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.36 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.7 Scenario 7: Alternative treatment effect of cerliponase alfa on health state utilities*

Table 36 presents the cost-effectiveness results of scenario 7, where the EAG uses an alternative approach to estimate the health state utilities for SoC using evidence from the MAA and Gissen et al., 2021.[1]

**Table 36 Cost-effectiveness results for scenario 7: Alternative treatment effect of cerliponase alfa on health state utilities**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company scenario: 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 | | | | |
| Cerliponase alfa | [redacted] | 15.32 | [redacted] | 16.20 | [redacted] | £300,000 |
| **Scenario 7: 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 | | | | |
| Cerliponase alfa | [redacted] | 15.62 | [redacted] | 15.51 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.8 Scenario 8: Impact of cerliponase alfa on care and siblings disutilities*

Table 37 presents the cost-effectiveness results of scenario 8, where the EAG applies alternative (more conservative) carer and sibling disutility estimates for cerliponase alfa compared to the company's base-case.

**Table 37 Cost-effectiveness results for scenario 8: Impact of cerliponase alfa on care and siblings disutilities**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Carer and sibling disutilities for cerliponase alfa correspond to 50% of the SoC values** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 8.1: Carer and sibling disutilities for cerliponase alfa are the same as for the SoC values** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.87 | [redacted] | 17.15 | [redacted] | £300,000 |
| **Scenario 8.2: Carer and sibling disutilities for cerliponase alfa correspond to 75% of the SoC values** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.97 | [redacted] | 17.25 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.9 Scenario 9: Including ECG costs*

Table 38 presents the cost-effectiveness results of scenario 9, where the EAG includes the costs of ECG monitoring in line with the NICE committee's preferences for the original HST12.

**Table 38 Cost-effectiveness results for scenario 9: Including ECG costs**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: excluding ECG monitoring costs** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 9: Including ECG monitoring costs** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; ECG, electrocardiogram; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.10 Scenario 10: No impact of cerliponase alfa on progressive symptoms other than seizures*

Table 39 presents the cost-effectiveness results of scenario 9, where the EAG applies the same estimates of resource use for progressive symptoms other than seizures for both treatment groups.

**Table 39 Cost-effectiveness results for scenario 10: No impact of cerliponase alfa on progressive symptoms other than seizures**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Proportion of patients with progressive symptoms (other than seizures) as elicited from company's clinical experts** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 10.1: 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 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 10.2: 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 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CA, Cerliponase alfa; CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

#### *6.2.1.11 Scenario 11: Including psychiatric/ behavioural support costs*

Table 40 presents the cost-effectiveness results of scenario 11, where the EAG includes the costs of psychiatric/behavioural support in line with the NICE committee's preferences for the original HST12.

**Table 40 Cost-effectiveness results for scenario 11: Including psychiatric/behavioural support costs**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Excluding psychiatric/behavioural support costs** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 11: Including psychiatric/behavioural support costs** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

### *6.3 EAG's preferred assumptions*

This section presents the results of the EAG's analyses that incorporated into the EAG's base case analysis.

The EAG preferred assumptions which differ from those of the company are the following:

1. Baseline characteristics according to the NICE committee's preference for the original HST12
2. The proportion of patients treated with cerliponase alfa assumed to be initial stabilisers corresponds to 80% of those entering the model in health state 1
3. Transition probabilities in health states 1-9 are informed by the 'all patients' pooled dataset
4. Vision loss modelled according to the NICE committee's preference for the original HST12
5. Neuro-disability related mortality applies to patients in health state 1-9
6. Cerliponase alfa treatment discontinuation when patients transition to health state 7
7. ECG monitoring costs are included
8. Psychiatric/behavioural support costs are included

The EAG believes that the company's preferred evidence source to inform the baseline characteristics of the model population (Study 190-203, younger than 3 years subgroup) is unlikely to reflect the average population eligible for treatment with cerliponase alfa in the NHS currently and/or in the next five years, given clinical advice received. The EAG preferred assumption corresponds to the NICE committee's preferred assumption for these parameters (see scenario 1.3), which is still more optimistic towards the cost-effectiveness of cerliponase alfa than the estimates using the estimates informed by clinical opinion received by the EAG.

The EAG considers the company's assumption that all patients treated with cerliponase alfa who enter the model at health state 1 are initial stabilisers too optimistic, as there is evidence that [redacted] (see Section 4.2.7.1). Given the small numbers of patients across studies overall and the limited duration of follow-up in Study 190-203 with only some patients being followed up to 6 years, it is very uncertain whether all patients with a ML score of 0 are initial stabilisers. As noted by the EAG in Section 3.9, it is also possible that, because patients diagnosed at ML score of 6 are likely to be younger at time of diagnosis, the slower rate in decline in these patients is at least partly attributable to the fact that decline would not start immediately (even without cerliponase alfa). The clinical adviser to the EAG also considered that while the 6 years duration of stabilisation appears to be clinically plausible for the majority of patients initiating treatment at ML score of 0, the proportion of these patients who will have such a treatment response is uncertain and unlikely to be 100%. Thus, the EAG preferred assumption reflects the views of our clinical adviser, who suggested that 80% would be a more appropriate value for this parameter.

As discussed in Section 4.2.7.1, the EAG considers that the 'all patients' pooled dataset (matched to Study 190-901) is the most appropriate source of evidence to inform the transition probabilities in health states 1-7, because this source reflects the majority of existing evidence for these parameters due to sample size and overall length of follow-up.

For assumptions 4 to 9 the EAG considers that there is insufficient clinical evidence to support deviating from the NICE committee's preference for the original HST12, and therefore, the EAG preferred assumptions match these previously referred assumption. The EAG also notes that there is some variability in when treatment with cerliponase alfa is discontinued in clinical practice, but the company implementation of treatment effects implies a maintenance of cerliponase alfa treatment effect on the transition probability from health state 6 (probability of remaining on that health state or moving to health state 5). As discussed in Section 4.2.8nder the company's base case assumptions, individuals will remain on health state 6 without receiving cerliponase alfa for on average 3.2 years under the company's base assumption, which may suggest a long maintenance of treatment effect. Furthermore, because transitions from health state 6 to 5 are allowed, this also means that some patients can reinitiate treatment with cerliponase alfa when they move to health state 5, which may also be unlikely.

As in Section 6.2, all presented results are based on a deterministic analysis, except for the EAG's base case analysis for which deterministic and probabilistic results are presented in Table 41 and Table 42, respectively. Table 41 also illustrates the cumulative impact of the analyses that the EAG undertook in developing the EAG's base case. In the EAG's deterministic base-case both the incremental costs and incremental QALYs for cerliponase alfa vs. SoC decreased compared to the compared to the company's base-case ([redacted] vs. [redacted]; 9.91 vs. 17.35 QALYs), suggesting in an ICER of [redacted] per additional QALY. The EAG note that under our base-case assumptions the undiscounted LYs are 37.26 LYs (with approximately 11 years, on average, spent in health state 1) for cerliponase alfa. The shorter life expectancy and shorter time on treatment with cerliponase alfa largely explain the impact on the estimates of cost-effectiveness. The applicable cost-effectiveness threshold is also reduced to £169,561 per additional QALY, due to the EAG base-case analysis suggesting 16.96 undiscounted incremental QALYs for cerliponase alfa vs. SoC.

**Table 41 Deterministic cost-effectiveness results for the EAG's preferred assumptions**

| Preferred assumption | Total Costs | Total QALYs | Incr. cost | Incr. QALYs | Cumulative ICER £/QALY | CE threshold* £/QALY | Section in EAR |
|---|---|---|---|---|---|---|---|
| **1. Company's base case** | | | | | | | |
| SoC | [redacted] | -0.28 | | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 | |
| **2. Analysis 1 + Baseline characteristics as per original HST12** | | | | | | | |
| SoC | [redacted] | -0.59 | | | | | |
| Cerliponase alfa | [redacted] | 13.25 | [redacted] | 13.84 | [redacted] | £271,374 | |
| **3. Analysis 2 + 80% of patients in HS1 are initial stabilisers** | | | | | | | |
| SoC | [redacted] | -0.59 | | | | | |
| Cerliponase alfa | [redacted] | 12.64 | [redacted] | 13.23 | [redacted] | £253,553 | |
| **4. Analysis 3 + transition probabilities health state 1-7 informed by 'all patient dataset'** | | | | | | | |
| SoC | [redacted] | -0.72 | | | | | |
| Cerliponase alfa | [redacted] | 8.82 | [redacted] | 9.54 | [redacted] | £152,674 | |
| **5. Analysis 4 + Vision loss as per original HST12** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | |
| Cerliponase alfa | [redacted] | 8.33 | [redacted] | 9.01 | [redacted] | £146,096 | |
| **6. Analysis 5 + Neuro-disability mortality applies to HS1-9** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | |
| Cerliponase alfa | [redacted] | 8.32 | [redacted] | 9.00 | [redacted] | £144,930 | |
| **7. Analysis 6 + Treatment discontinuation at HS7** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |
| **8. Analysis 7 + Including ECG costs** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |
| **9. EAG base case: Analysis 8 + Including psychiatric/behavioural support costs** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; EAR, external assessment group report; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 42 Probabilistic cost-effectiveness results for the EAG's preferred assumptions**

| Preferred assumption | Total Costs | Total QALYs | Incr. costs | Incr. QALYs | ICER £/QALY |
|---|---|---|---|---|---|
| **Company's base case** | | | | | |
| SoC | [redacted] | -0.14 | | | |
| Cerliponase alfa | [redacted] | 17.50 | [redacted] | 17.64 | [redacted] |
| **9. EAG base case** | | | | | |
| SoC | [redacted] | -0.69 | | | |
| Cerliponase alfa | [redacted] | 9.26 | [redacted] | 9.94 | [redacted] |

**Abbreviations**: ICER: incremental cost-effectiveness ratio; Inc., incremental; QALY: quality-adjusted life year

When considering the probabilistic results of the EAG's base case analysis, the interpretation of the cost-effectiveness estimates remains the same as for the deterministic ones (Table 41).

### *6.4 Further scenario analysis over the EAG's preferred assumptions*

The EAG also explored the impact of several assumptions over the EAG's base case, the results of which are presented in Table 43. The following additional assumptions over the EAG base case were explored, as they remain areas of uncertainty with impact on the estimates of cost-effectiveness:

- Baseline distribution
- Evidence source for transition probabilities in health states 1-9
- Discontinuation rule
- Treatment independent health state utilities
- Vision loss: age dependent

**Table 43 Cost-effectiveness results for further scenario analysis over the EAG's preferred assumptions**

| Preferred assumption | Total Costs | Total QALYs | Incr. cost | Incr. QALYs | Cumulative ICER £/QALY | CE threshold* £/QALY | Section in EAR |
|---|---|---|---|---|---|---|---|
| **Company's base case** | | | | | | | |
| SoC | [redacted] | -0.28 | | | | | 5.1.1 |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 | |
| **EAG base-case** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 6.1.1 |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |
| **1. EAG base-case + Baseline characteristics as per company's base-case** | | | | | | | |
| SoC | [redacted] | -0.46 | | | | | 4.2.4 |
| Cerliponase alfa | [redacted] | 12.38 | [redacted] | 12.84 | [redacted] | £228,459 | |
| **2. EAG base-case + Baseline characteristics as per clinical opinion of current practice in 5-year time** | | | | | | | |
| SoC | [redacted] | -0.75 | | | | | 4.2.4 |
| Cerliponase alfa | [redacted] | 8.98 | [redacted] | 9.72 | [redacted] | £166,626 | |
| **3. EAG base-case + Transition probabilities health state 1-7 as per company's base-case** | | | | | | | |
| SoC | [redacted] | -0.56 | | | | | 4.2.7.2 |
| Cerliponase alfa | [redacted] | 12.77 | [redacted] | 13.33 | [redacted] | £267,241 | |
| **4. EAG base case + Treatment discontinuation at HS6 as per company's base-case** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 4.2.8 |
| Cerliponase alfa | [redacted] | 8.32 | [redacted] | 9.00 | [redacted] | £144,930 | |
| **5. EAG base-case + Treatment independent health state utilities based on Gissen 2021** | | | | | | | |
| SoC | [redacted] | -0.33 | | | | | 4.2.10.2 |
| Cerliponase alfa | [redacted] | 8.51 | [redacted] | 8.85 | [redacted] | £149,215 | |
| **6. EAG base-case + Vision loss: age dependent and with linear decline until age of 10** | | | | | | | |
| SoC | [redacted] | -0.70 | | | | | 4.2.7.4 |
| Cerliponase alfa | [redacted] | 9.43 | [redacted] | 10.13 | [redacted] | £172,105 | |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

For the analysis that explore differences in preferred assumptions between the EAG and the company, those with the highest impact are: the baseline distribution of patients across health states (additional analysis 1; the source used to inform transitions (additional analysis 3) and the treatment discontinuation rule (additional analysis 4).

The EAG notes the considerable impact of additional analyses 5, where health state utilities are assumed to be treatment independent. While this an extreme scenario, the EAG thinks it is important to consider it alongside the EAG base-case, given the limitations of Gissen et al., 2021,[1] that this study is the sole source of comparative health state utility evidence between cerliponase alfa and SoC, and that the magnitude of the treatment effect of cerliponase alfa on health stat e HRQoL is uncertain.

### *6.5 Conclusions of the cost effectiveness section*

The economic evidence submitted by the company included an update of a model developed to assess the cost effectiveness of cerliponase alfa compared to SoC for the treatment of CLN2 in the original NICE appraisal of this treatment (HST12). The decision model was updated with evidence developed since the last appraisal of which the EAG highlights the following evidence sources as contributing the most to the updates:

1. Study 190-201/202, the key source of effectiveness in HST12 (96-week follow-up), has completed its follow-up (280 weeks on study)
2. The post-marketing study 190-203 was completed (169 weeks follow-up) - this was a study which aimed to develop clinical evidence in younger patients, including those younger than 2 years old;
3. MAA data collection including patients previously treated with cerliponase alfa in the company's clinical trial and new starters in the NHS (72 weeks follow-up);
4. Two company led advisory boards with clinical experts, which were used to inform several model parameters and to validate model assumptions.

The company's cost-effectiveness analyses, and further analyses conducted by EAG, at cerliponase alfa list price and at a provisional confidential PAS price, suggest that the ICER of cerliponase alfa vs. SoC lies considerably above the cost-effectiveness thresholds applicable in the context of the HST appraisal process. The EAG considers the economic evidence mostly comprehensive regarding relevant cost effectiveness studies and data included in the CS (exceptions are noted throughout Sections 1 and 4, and further EAG analyses are presented in Section 6). The assumptions and parameterisation choices with the most impact on ICER estimates were identified as:

- The evidence source used to inform the transition probabilities in health states 1-7;
- The baseline distribution of patients across health states;
- Whether vision loss progression for patients treated with cerliponase alfa is informed by i) disease progression with the SoC or ii) cerliponase alfa disease progression and age dependent vision loss;

- Treatment discontinuation for cerliponase alfa in health state 6 or 7.
- Magnitude of cerliponase alfa treatment effect on the patients' health state utilities.

All of the assumptions above are areas of uncertainty. Furthermore, there is also uncertainty on the structural link between motor and language disease progression which is driven by changes to the combined motor and language score to other key progression markers (developmental issues, seizures, requirement for a feeding tube, and palliative care). Due to this, observed clinical improvements and delay to progression as informed by the ML score result translate into impacts on other progression symptoms. The impact of the link between disease progression in terms of motor and language symptoms and progression in other disease symptoms not being established in this way, as well as the treatment effect of cerliponase alfa on the latter symptoms, are uncertain and difficult to validate, based on the evidence presented by the company. Furthermore, the treatment effect of cerliponase alfa on progressive symptoms is modelled in an inconsistent way between costs and HRQoL impacts. Progressive symptoms resource use by health state and treatment is directly informed by elicited clinical opinion, while the impact of these symptoms on patient HRQoL is not. Instead, progressive symptoms as described in health state vignettes are captured into the treatment specific health state utilities informed by a published study.[1] The description of progressive symptoms in the vignettes does not completely align with the elicited progressive symptoms resource use.
This model structure has previously been accepted by the NICE committee's to the original HST12, as appropriate to inform decision making. However, the EAG considers that the decision uncertainty associated with this structural feature has increased by applying additional (within health state) treatment effects for cerliponase alfa vs. SOC on progressive symptoms in this re-appraisal.

The following assumptions have considerable impact on reducing the applicable cost-effectiveness threshold (but a more modest impact on the ICERs), because they substantially reduce the incremental QALY gains for cerliponase alfa vs. SoC but also incremental costs (due to less time accruing the costs associated with cerliponase alfa):

- Transition probabilities after 6 years for initial stabilisers closer to those of non-stabilisers;
- Backward transitions to healthier states not allowed for both treatment groups.

Overall, the EAG considers that the company's base-case analysis ICER for cerliponase alfa vs. SoC, [redacted] per additional QALY is likely to be an underestimate. The EAG's base-case analysis suggests an ICER [redacted] per additional QALY. While the EAG's base-case analysis makes generally more conservative assumptions than the company's, the EAG notes that there are still unresolved uncertainties, particularly around the magnitude of cerliponase alfa treatment effect on the patients' health state utilities (and seizures), baseline distribution of patients across health states and

the robustness of the transition probabilities in health states 1-7 that can potentially increase the ICER for cerliponase alfa vs. SoC.

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# APPENDICES

## Appendix 1: Critiques of identification of clinical evidence

### Table 44 EAG appraisal of clinical evidence identification

| TOPIC | EAG RESPONSE | NOTE |
|---|---|---|
| Is the report of the search clear and comprehensive? | PARTLY | The documentation was mostly clear and comprehensive, with several exceptions.<br><br>In the original company submission, the following search strategies were missing: strategies for conference proceedings; health technology assessment sources; and clinical trial registries. This was raised as a PfC. In response, the company provided additional information about search terms used but these were not documented properly with details of the number of hits from each source.<br><br>There were several errors in the documentation:<br><br>• Medline's inception was listed as 1974 rather than 1946.<br><br>• The documentation of the original Cochrane Library searches used the syntax for the Wiley platform rather than the Ovid platform as documented.<br><br>• In the original searches of the Cochrane Library, line 10 was mistakenly blank and there was an error on line 11 where exp appeared at the end of a search line.<br><br>The initial Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram, Figure 1, was unclear and contained errors. Notably, 'congress' was vague and other conference proceedings were not listed; the searches of clinicaltrials.gov and health technology assessment (HTA) sources were not listed; there were searches of the European Medicines Agency listed even though these do not appear in the sources searched; and World Health Organization's International Clinical Trials Registry Platform appears twice. This was raised as a PfC. In response, the company were unable to provide any clarification as this related to the original systematic literature review conducted in 2018 and they did not have access to the supporting documents. |
| Were appropriate sources searched? | YES | A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases were used. However, although HTA sources were searched no dedicated HTA databases were searched. |
| Was the timespan of the searches appropriate? | YES | The original searches were not limited by date in the strategy. The only use of date limits was to remove conference abstracts older than the last 3 years and for the update searches. |
| Were appropriate parts of the PICOS included in the search strategies? | YES | The searches combined the condition with the study types. |
| Were appropriate search terms used? | YES | Search terms for the condition were comprehensive. |
| Were any search restrictions applied appropriate? | YES | Yes, animal studies and irrelevant paper types are removed appropriately. |
| Were any search filters used, validated and referenced? | UNCLEAR | No filters are referenced. |

# Appendix 2: Critiques of identification of cost-effectiveness evidence

**Table 45 EAG appraisal of evidence identification in the company's cost-effectiveness SLR**

| TOPIC | EAG RESPONSE | NOTE |
|---|---|---|
| **Is the report of the search clear and comprehensive?** | PARTLY | The documentation was mostly clear and comprehensive, with several exceptions.<br><br>In the original company submission, the following search strategies were missing: conference proceedings, health technology assessment (HTA) sources, and grey literature sources. In response to PfCs, the company provided additional information about search terms used but these were not documented properly with details of the number of hits from each source.<br><br>In Figure 1, EconLit wrongly listed 0 results instead of 1; 'congress' was vague and other conference proceedings were not listed; research papers in economics (RePEc) and the international health technology assessment database (INAHTA) were not listed; and some of the sources listed under 'supplementary database searches' were not databases. This was raised as a PfC. In response, the company were unable to provide any clarification as this related to the original SLR conducted in 2018 and they did not have access to the supporting documents. |
| **Were appropriate sources searched?** | YES | A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases were searched. |
| **Was the timespan of the searches appropriate?** | YES | The original searches were not limited by date in the strategy. The update searches limited by the date of the last search.<br><br>The EconLit searches were limited from 2017 onwards. However, this would not have missed any records since the database hits only shows 1 result before and after the application of this limit. |
| **Were appropriate parts of the PICOS included in the search strategies?** | YES | The searches combined the condition with the study types. |
| **Were appropriate search terms used?** | YES | Search terms were comprehensive. |

| | | |
|---|---|---|
| **Were any search restrictions applied appropriate?** | PARTLY | Yes, animal studies and irrelevant paper types are removed appropriately.<br><br>The searches of NHS EED and HTA via the Cochrane Library databases on the Wiley platform applied inappropriate limits to filter results by technology assessments and economic evaluations. This was raised as a PfC. In response, the company were unable to provide any clarification as this related to the original SLR conducted in 2018 and they did not have access to the supporting documents. |
| **Were any search filters used validated and referenced?** | YES | Search filters were used and referenced but not validated. |

**EAG response =** YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

**Table 46 EAG appraisal of evidence identification in the company's HRQoL SLR**

| TOPIC | EAG RESPONSE | NOTE |
|---|---|---|
| **Is the report of the search clear and comprehensive?** | PARTLY | The documentation was mostly clear and comprehensive, with several exceptions.<br><br>In the original company submission, the following search strategies were missing: conference proceedings, HTA sources, and grey literature sources. In response to PfCs, the company provided additional information about search terms used but these were not documented properly with details of the number of hits from each source.<br><br>In Figure 1, EconLit wrongly listed 0 results instead of 1; 'congress' was vague and other conference proceedings were not listed; research papers in economics (RePEc) and the international health technology assessment database (INAHTA) were not listed; and some of the sources listed under 'supplementary database searches' were not databases. This was raised as a PfC. In response, the company were unable to provide any clarification as this related to the original SLR conducted in 2018 and they did not have access to the supporting documents. |
| **Were appropriate sources searched?** | YES | A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases were searched. |
| **Was the timespan of the searches appropriate?** | YES | The original searches were not limited by date in the strategy. The update searches limited by the date of the last search. |

| | | |
|---|---|---|
| | | The EconLit searches were limited from 2017 onwards. However, this wouldn't have missed any records since the database hits only shows 1 result before and after the application of this limit. |
| **Were appropriate parts of the PICOS included in the search strategies?** | YES | The searches combined the condition with the study types. |
| **Were appropriate search terms used?** | YES | Search terms were comprehensive. |
| **Were any search restrictions applied appropriate?** | PARTLY | Yes, animal studies and irrelevant paper types are removed appropriately.<br><br>The searches of NHS EED and HTA via the Cochrane Library databases on the Wiley platform applied inappropriate limits to filter results by technology assessments and economic evaluations. This was raised as a PfC. In response, the company were unable to provide any clarification as this related to the original SLR conducted in 2018 and they did not have access to the supporting documents. |
| **Were any search filters used validated and referenced?** | YES | Search filters were used and referenced but not validated. |

**EAG response =** YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

**Table 47 EAG appraisal of evidence identification in the company's costs and resource use SLR**

| TOPIC | EAG RESPONSE | NOTE |
|---|---|---|
| **Is the report of the search clear and comprehensive?** | PARTLY | The documentation was mostly clear and comprehensive, with several exceptions.<br><br>In the original company submission, the following search strategies were missing: conference proceedings, health technology assessment (HTA) sources, and grey literature sources. In response to PfCs, the company provided additional information about search terms used but these were not documented properly with details of the number of hits from each source.<br><br>In Figure 1, EconLit wrongly listed 0 results instead of 1; 'congress' was vague and other conference proceedings were not listed; research papers in economics (RePEc) and the international health technology assessment database (INAHTA) were not listed; and some of the |

| | | |
|---|---|---|
| | | sources listed under 'supplementary database searches' were not databases. This was raised as a PfC. In response, the company were unable to provide any clarification as this related to the original SLR conducted in 2018 and they did not have access to the supporting documents. |
| **Were appropriate sources searched?** | YES | A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases were searched. |
| **Was the timespan of the searches appropriate?** | YES | The original searches were not limited by date in the strategy. The update searches limited by the date of the last search.<br><br>The EconLit searches were limited from 2017 onwards. However, this wouldn't have missed any records since the database hits only shows 1 result before and after the application of this limit. |
| **Were appropriate parts of the PICOS included in the search strategies?** | YES | The searches combined the condition with the study types. |
| **Were appropriate search terms used?** | YES | Search terms were comprehensive. |
| **Were any search restrictions applied appropriate?** | PARTLY | Yes, animal studies and irrelevant paper types are removed appropriately.<br><br>The searches of NHS EED and HTA via the Cochrane Library databases on the Wiley platform applied inappropriate limits to filter results by technology assessments and economic evaluations. This was raised as a PfC. In response, the company were unable to provide any clarification as this related to the original SLR conducted in 2018 and they did not have access to the supporting documents. |
| **Were any search filters used validated and referenced?** | YES | Search filters were used and referenced but not validated. |

# Appendix 3: Resource use

**Table 48: Costs associated with the treatment of progressive symptoms (adapted from Table 69-79, CS).**

| Treatment | Annual cost of medications | | Proportion of medication usage | | Total cost per year | Evidence source |
|---|---|---|---|---|---|---|
| Anti-epileptic drugs (AED) | VI | £63.58 | VI | 17% | £77.42 | The types of medication and their distribution were taken from patient narratives in Studies 190-202 [42] |
| | Lm | £1.93 | Lm | 0% | | |
| | Lv | £0.72 | Lv | 4% | | |
| | Tp | £12.92 | Tp | 0% | | |
| | Cb | £9.42 | Cb | 0% | | |
| | Zn | £3.79 | Zn | 0% | | |
| | Cn | £123.81 | Cn | 0% | | |
| | Vl + Lv | £64.30 | Vl + Lv | 17% | | |
| | Vl + Lv + Zn | £68.09 | Vl + Lv + Zn | 4% | | |
| | Vl + Lv + Cn | £188.11 | Vl + Lv + Cn | 9% | | |
| | Vl + Lv + Lm | £66.23 | Vl + Lv + Lm | 4% | | |
| | Vl + Lm + Zn | £69.31 | Vl + Lm + Zn | 4% | | |
| | Vl + Lm + Cb | £74.93 | Vl + Lm + Cb | 9% | | |
| | Vl + Lm + Tp | £78.43 | Vl + Lm + Tp | 4% | | |
| | Vl + Zn + Cb | £76.79 | Vl + Zn + Cb | 13% | | |
| | Vl + Cn + Tp | £200.31 | Vl + Cn + Tp | 4% | | |
| | Lv + Zn + Cb | £13.93 | Lv + Zn + Cb | 4% | | |
| | Lv + Lm + Tp | £15.57 | Lv + Lm + Tp | 4% | | |
| Distress | Acetaminophen | £25.71 | Acetaminophen | 14% | £89.73 | The list of medications was derived from Williams et al, 2017 [40]<br><br>Assumed that all medications were equally likely to be used. |
| | Methadone | £137.40 | Methadone | 14% | | |
| | Morphine | £24.57 | Morphine | 14% | | |
| | Hydromorphone | £345.16 | Hydromorphone | 14% | | |
| | Amitriptyline | £1.53 | Amitriptyline | 14% | | |
| | Gabapentin | £0.04 | Gabapentin | 14% | | |
| | Pregabalin | £93.70 | Pregabalin | 14% | | |
| Dystonia | Baclofen | £0.55 | Baclofen | 33.3% | £13.39 | The list of medications was derived from Williams et al, 2017 [40]<br><br>Assumed that all medications were equally likely to be used. |
| | Clonidine | £34.00 | Clonidine | 33.3% | | |
| | Trihexyphenidyl | £5.61 | Trihexyphenidyl | 33.3% | | |

| | | | | |
|---|---|---|---|---|
| | | | | Only these three medications applied as other medications also used to treat epilepsy |
| Myoclonus | Phenobarbital £102.96 | Phenobarbital 100% | £102.96 | The list of medications was derived from Williams et al, 2017 [40]<br><br>Only phenobarbital applied as other medications also used to treat epilepsy |
| Musculoskeletal pain | It is anticipated the medications used for musculoskeletal pain are the same as those used to treat other progressive symptoms. No additional costs have therefore been modelled. | | | |
| Feeding tube | Insertion costs have not been modelled as it is anticipated that all patients will require feeding tube insertion during their lifetime.<br><br>Replacement cost £676.92 | - | £676.92 | Replaced every two years |
| Chronic seizures | Rectal diazepam £1.00<br>Intravenous lorazepam £8.30<br>Buccal midazolam £0.10<br>Intravenous phenobarbital £96.27<br>Hospitalisation £1,003.13 | Rectal diazepam 48.9%<br>Intravenous lorazepam 40.9%<br>Buccal midazolam 5.8%<br>Intravenous phenobarbital 4.4%<br>Hospitalisation 45.3% | £462.07 | Medication usage from Study 190-201/202 [42]<br><br>Hospitalisation for cases where intravenous rescue medication required (45.3%) |

Abbreviations: Cb: Clobazam; Cn: Clonazepam; Lm: Lamotrigine; Lv: Levetiracetam; Tp: Topiramate; VI: Sodium valproate; Zn: Zonisamide.

# Appendix 4: Additional cost effectiveness results at provisional PAS price

This section presents the EAG's cost-effectiveness analyses results, corresponding to the analyses reported in Section 6, and applying a provisional PAS price of [redacted]% over cerliponase alfa's list price. The interpretation of these results is broadly the same as in Section 6, despite the lower acquisition cost for cerliponase alfa.

**Table 49 Cost-effectiveness results for scenario 1 (provisional PAS price) – Baseline characteristics**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: As per Study 190-203, < 3 years (HS1: 87.5%, HS2: 12.5%; age 2 years)** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 1.1: Current clinical practice (HS1: 15%, HS2: 45%, HS3: 30%, HS4:10%; age 4.5 years)** | | | | | | |
| SoC | [redacted] | -1.10 | | | | |
| Cerliponase alfa | [redacted] | 7.77 | [redacted] | 8.86 | [redacted] | £156,189 |
| **Scenario 1.2: Clinical practice in 5-year time HS1: 50%, HS2: 35%, HS3: 12.5%, HS4:2.5%; age 3.5 years)** | | | | | | |
| SoC | [redacted] | -0.67 | | | | |
| Cerliponase alfa | [redacted] | 12.56 | [redacted] | 13.23 | [redacted] | £260,474 |
| **Scenario 1c: As per original HST12 (HS1:50%, HS2: 50%; age 4 years)** | | | | | | |
| SoC | [redacted] | -0.59 | | | | |
| Cerliponase alfa | [redacted] | 13.25 | [redacted] | 13.84 | [redacted] | £271,374 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 50 Cost-effectiveness results for scenario 2 (provisional PAS price): Stabilisation assumption - proportion of initial stabilisers**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: 100% of patients in HS1 at model entrance are initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 2: 80% of patients in HS1 at model entrance are initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.02 | [redacted] | 16.30 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 51 Cost-effectiveness results for scenario 3 (provisional PAS price): Stabilisation assumption - reduction in transition probabilities after initial stabilisation**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: 50% progression multiplier for initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 3.1: 0% progression multiplier for initial stabilisers** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 14.05 | [redacted] | 14.34 | [redacted] | £249,379 |
| **Scenario 3.2: 75% progression multiplier for initial stabilisers** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 15.37 | [redacted] | 15.66 | [redacted] | £295,302 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

### Table 52 Cost-effectiveness results for scenario 4 (provisional PAS price): Backwards transitions to healthier states not allowed

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Backward transitions to healthier states allowed for cerliponase alfa only (HS 1-7)** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 4: Backwards transitions to healthier states not allowed** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 12.09 | [redacted] | 12.38 | [redacted] | £194,039 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 53 Cost-effectiveness results for scenario 5 (provisional PAS price): Vision loss**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case – linear decline with age between 6 and 20 years old** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 5.1: Linear decline with age between 6 and 10 years old** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.57 | [redacted] | 16.85 | [redacted] | £300,000 |
| **Scenario 5.2: as per original HST12 (driven by cumulative proportion of vision loss in the SoC)** | | | | | | |
| SoC | [redacted] | -0.26 | | | | |
| Cerliponase alfa | [redacted] | 16.20 | [redacted] | 16.45 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 54 Cost-effectiveness results for scenario 6 (provisional PAS price): Neuro-disability mortality included for health states 6-9**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Neuro-disability mortality excluded** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 6: neuro-disability mortality included for HS6-9** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.36 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 55 Cost-effectiveness results for scenario 7 (provisional PAS price): Alternative treatment effect of cerliponase alfa on health state utilities**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company scenario: 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 | | | | |
| Cerliponase alfa | [redacted] | 15.32 | [redacted] | 16.20 | [redacted] | £300,000 |
| **Scenario 7: 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 | | | | |
| Cerliponase alfa | [redacted] | 15.62 | [redacted] | 15.51 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 56 Cost-effectiveness results for scenario 8 (provisional PAS price): Impact of cerliponase alfa on care and siblings disutilities**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Carer and sibling disutilities for cerliponase alfa correspond to 50% of the SoC values** | | | | | | |
| SoC | [redacted] | -0.28 | - | - | - | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 8.1: Carer and sibling disutilities for cerliponase alfa are the same as for the SoC values** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.87 | [redacted] | 17.15 | [redacted] | £300,000 |
| **Scenario 8.2: Carer and sibling disutilities for cerliponase alfa correspond to 75% of the SoC values** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 16.97 | [redacted] | 17.25 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 57 Cost-effectiveness results for scenario 9 (provisional PAS price): Including ECG costs**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: excluding ECG monitoring costs** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 9: Including ECG monitoring costs** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; ECG, electrocardiogram; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 58 Cost-effectiveness results for scenario 10 (provisional PAS price): No impact of cerliponase alfa on progressive symptoms other than seizures**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Proportion of patients with progressive symptoms (other than seizures) as elicited from company's clinical experts** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 10.1: 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 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 10.2: 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 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CA, Cerliponase alfa; CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 59 Cost-effectiveness results for scenario 11 (provisional PAS price): Including psychiatric/behavioural support costs**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (/QALY) | CE threshold* (/QALY) |
|---|---|---|---|---|---|---|
| **Company base case: Excluding psychiatric/behavioural support costs** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |
| **Scenario 11: Including psychiatric/behavioural support costs** | | | | | | |
| SoC | [redacted] | -0.28 | | | | |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 60 Deterministic cost-effectiveness results for the EAG's preferred assumptions (provisional PAS price)**

| Preferred assumption | Total Costs | Total QALYs | Incr. cost | Incr. QALYs | Cumulative ICER £/QALY | CE threshold* £/QALY | Section in EAR |
|---|---|---|---|---|---|---|---|
| **1. Company's base case** | | | | | | | |
| SoC | [redacted] | -0.28 | | | | | 5.1.1 |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 | |
| **2. Analysis 1 + Baseline characteristics as per original HST12** | | | | | | | |
| SoC | [redacted] | -0.59 | | | | | 4.2.4 |
| Cerliponase alfa | [redacted] | 13.25 | [redacted] | 13.84 | [redacted] | £271,374 | |
| **3. Analysis 2 + 80% of patients in HS1 are initial stabilisers** | | | | | | | |
| SoC | [redacted] | -0.59 | | | | | 4.2.7.1 |
| Cerliponase alfa | [redacted] | 12.64 | [redacted] | 13.23 | [redacted] | £253,553 | |
| **4. Analysis 3 + transition probabilities health state 1-7 informed by 'all patient dataset'** | | | | | | | |
| SoC | [redacted] | -0.72 | | | | | 4.2.7.1 |
| Cerliponase alfa | [redacted] | 8.82 | [redacted] | 9.54 | [redacted] | £152,674 | |
| **5. Analysis 4 + Vision loss as per original HST12** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 4.2.7.4 |
| Cerliponase alfa | [redacted] | 8.33 | [redacted] | 9.01 | [redacted] | £146,096 | |
| **6. Analysis 5 + Neuro-disability mortality applies to HS1-9** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 4.2.7.5 |
| Cerliponase alfa | [redacted] | 8.32 | [redacted] | 9.00 | [redacted] | £144,930 | |
| **7. Analysis 6 + Treatment discontinuation at HS7** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 4.2.8 |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |
| **8. Analysis 7 + Including ECG costs** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 4.2.11.5 |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |
| **9. EAG base case: Analysis 8 + Including psychiatric/behavioural support costs** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 4.2.11.12 |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviations: HS, health state; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

**Table 61 Cost-effectiveness results for further scenario analysis over the EAG's preferred assumptions (provisional PAS price)**

| Preferred assumption | Total Costs | Total QALYs | Incr. cost | Incr. QALYs | Cumulative ICER £/QALY | CE threshold* £/QALY | Section in EAR |
|---|---|---|---|---|---|---|---|
| **Company's base case** | | | | | | | |
| SoC | [redacted] | -0.28 | | | | | 5.1.1 |
| Cerliponase alfa | [redacted] | 17.07 | [redacted] | 17.35 | [redacted] | £300,000 | |
| **EAG base-case** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 6.1.1 |
| Cerliponase alfa | [redacted] | 9.23 | [redacted] | 9.91 | [redacted] | £169,561 | |
| **1. EAG base-case + Baseline characteristics as per company's base-case** | | | | | | | |
| SoC | [redacted] | -0.46 | | | | | 4.2.4 |
| Cerliponase alfa | [redacted] | 12.38 | [redacted] | 12.84 | [redacted] | £228,459 | |
| **2. EAG base-case + Baseline characteristics as per clinical opinion of current practice in 5-year time** | | | | | | | |
| SoC | [redacted] | -0.75 | | | | | 4.2.4 |
| Cerliponase alfa | [redacted] | 8.98 | [redacted] | 9.72 | [redacted] | £166,626 | |
| **3. EAG base-case + Transition probabilities health state 1-7 as per company's base-case** | | | | | | | |
| SoC | [redacted] | -0.56 | | | | | 4.2.7.1 |
| Cerliponase alfa | [redacted] | 12.77 | [redacted] | 13.33 | [redacted] | £267,241 | |
| **4. EAG base case + Treatment discontinuation at HS6 as per company's base-case** | | | | | | | |
| SoC | [redacted] | -0.68 | | | | | 4.2.8 |
| Cerliponase alfa | [redacted] | 8.32 | [redacted] | 9.00 | [redacted] | £144,930 | |
| **5. EAG base-case + Treatment independent health state utilities based on Gissen 2021** | | | | | | | |
| SoC | [redacted] | -0.33 | | | | | 4.2.10.3 |
| Cerliponase alfa | [redacted] | 8.51 | [redacted] | 8.85 | [redacted] | £149,215 | |
| **6. EAG base-case + Vision loss: age dependent and with linear decline until age of 10** | | | | | | | |
| SoC | [redacted] | -0.70 | | | | | 4.2.7.4 |
| Cerliponase alfa | [redacted] | 9.43 | [redacted] | 10.13 | [redacted] | £172,105 | |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

Abbreviation: CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Highly Specialised Technology**

**Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]**

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 19 April** using the below comments table.

All factual errors will be highlighted in a report and presented to the evaluation committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'REDACTED' should be highlighted in turquoise and all information submitted as 'REDACTED' in pink.

**Issue 1 Points of clarification**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 2.3.1, page 30 | Change from<br>"Four CLN2 patients in study 109-201/202 and all 35 CLN2 patients in the MAA study were from the UK."<br>to<br>"**All 35 CLN2 patients in the MAA study, which included one participant that transitioned from Study 190-203, four from Study 190-201/202, and six from Study 190-502, were from the UK**." | The company suggests that the EAG report text is amended to provide additional clarification, explaining that the patients from study 190-201/202 and the MAA were not mutually exclusive. Further details are suggested to accurately reflect the patient flow from all clinical trials for cerliponase alfa to the MAA FAS. | Amended as suggested |
| EAG report, Section 3.2.1, page 37, Table 3 | Change dose listed for all studies (except 190-901) in Table 3 to "According to SmPC: 300mg for aged ≥ 2 years. 100–200mg for up to 2 years, dependent on age" | All the included studies treated participants according to the approved dose listed in the SmPC.<br>Although the table is not inaccurate, as all participants were aged ≥2 years where a 300mg dose is stated, the current dose column is misleading as it reflects different cerliponase alfa dosing used across the evidence base. | Amended as suggested |
| EAG report, Section 3.4.1, page 46 | Change from<br>"[redacted]" | To accurately reflect what is stated in the CS (Document B, Section B.2.10.1), the sentence should | Not a factual inaccuracy. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | to<br>“[redacted]” | clearly indicate that the event occurred outside of the MAA reporting period that was presented in the CS. | |
| EAG report, Section 3.4.7, page 51, Table 8 | Change from<br>“PedsQL Family Impact Module: Mean (SD) total score change from baseline was [redacted] (n=12) at 18 months and [redacted] at 48 months (n=4)<br>CLN2-QoL: Total score change from baseline was [redacted] (n=13) at 18 months and [redacted] at 48 months (n=4)”<br>to<br>“PedsQL Family Impact Module: Mean (SD) total score change from baseline was [redacted] (n=12) at 18 months and [redacted] at 48 months (n=4)<br>CLN2-QoL: Total score change from baseline was [redacted] (n=13) at 18 months and [redacted] at 48 months (n=4)” | Standard deviation is inconsistently reported for every timepoint | Amended as suggested |
| EAG report, Section 3.6, page 54 | Change from:<br>“The CS reported indirect comparisons of cerliponase alfa patients with natural | The term typically used to describe this type of analysis would be 1:1 matching. | Not a factual inaccuracy. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | history patients from trial 190-901 using patient-to-patient matching".<br>to<br>"The CS reported indirect comparisons of cerliponase alfa patients with natural history patients from trial 190-901 using **1:1** matching". | | |
| EAG report, Section 3.8, page 55 | The company suggest that the text is edited to clarify which data were used (cerliponase alfa treated patients, matched patients):<br>"Using the individual-level data on ML score we plotted the mean decline in score over time according to ML score at treatment initiation (see Figure 7)." | To clarify which data were used in the EAG's analysis. | We have added more detail on this in Section 3.8 (Page 54-55). |
| EAG report, Section 3.8, page 55 | Change from:<br>"However, given the limited data, and the suggestion of a non-linear trend in Figure 7, this finding should be interpreted with caution."<br>to<br>"However, given the limited data~~, and the suggestion of a non-linear trend in Figure~~ | Asserting a non-linear trend is difficult, especially given that this conclusion stems from data from just two patients (or from one patient if the matched population was used). | Not a factual inaccuracy.<br>We are not asserting that there is a non-linear trend here: hence the use of "suggestion". |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | ~~7~~, this finding should be interpreted with caution.” | | |
| EAG report, Section 3.8, page 56, Figure 7 | The company has noted that Figure 7 is difficult to interpret and potentially misleading. The company therefore request that an alternative approach to illustrating this information be used. | The company has noted that Figure 7 is difficult to follow and may be misleading. Firstly, it is not entirely clear which studies were used to inform this data, as the size of lines used does not align with 40 matched patients.<br>The company would like to highlight that the ML score of 6 bar is misleading. Although the line becomes thinner due to the participant size becoming smaller with extra follow-up, this is not sufficiently clear and could suggest a deterioration in all patients with an ML score of 6 after 4 years. | Not a factual inaccuracy.<br>The data used for Figure 7 is now fully described on pages 54-55. |
| EAG report, Section 3.8, page 56 | The company notes that it is not clear which populations are included in the cohorts represented in Figure 8.<br>(“Figure 8 shows the Kaplan-Meir curve for a 2-pont decline in ML score (this are not necessarily “unreversed” decline) separately for each of the three study cohorts.”) | To clarify whether ‘MAA’ in Figure 8 represents MAA FAS, MAA new starter patients only, and whether ex-trial MAA patients were plotted in two cohorts. | This is the data as supplied in the clarification document as Figure 34. We assume therefore that this is the MAA FAS. This is clarified at page 54-55. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 4.1, page 63, Table 12 | Change from<br>"Linear progression to complete vision loss between 6 and 20 years of age for both cerliponase alfa and SoC"<br>to<br>"Linear progression to complete vision loss between 6 and 20 years of age for both cerliponase alfa and SoC **in health states 1–6, and vision loss assumed for all patients in health states 7–9**" | To accurately reflect how vision loss is modelled in health states 7–9. | The EAG has amended the text and stated:<br>"Linear progression to complete vision loss between 6 and 20 years of age for both cerliponase alfa and SoC **in health states 1–6, and vision loss assumed for all patients in health states 7–9**" |
| EAG report, Section 4.2.1., page 65 | The EAG noted that they identified two additional HTA submissions for cerliponase alfa for the treatment of CLN2 disease. The company would like to clarify that these additional HTAs are a PBAC and NCPE submission, which were not identified as the company only hand searched UK HTA agencies. The company suggests that the EAG report text be amended to clarify that these submissions were not included due to the methodology outlined in Appendix G of the CS. | To clarify why the additional HTA submissions were not included in the CS. | Not a factual inaccuracy. The point the EAG is making is that the searches used by the company may have missed relevant HTAs and this is supported by the fact that HTAs considered relevant were not identified. The EAG does not make comments on why the search strategy did not identify this (e.g., if by design or other reason).<br>Furthermore, the company state here that they only searched UK HTAs, which could justify why they did not identify the PBAC and NCPE submissions. However, the one of the HTA submissions |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | | identified by the company include a CADTH submission, and, therefore, a non-UK HTA. So it is still not clear why HTAs from other countries were not included (or considered reliable by the company).<br><br>The EAG has, notwithstanding, adapted the text to make it clearer that these references were not included and are considered relevant by the EAG.<br><br>The EAG considers that the searches were comprehensive and likely to have identified all relevant published cost-effectiveness studies but might have missed relevant HTA submissions. In addition to the two HTAs[34, 35] included in the company's SLR, the EAG identified two other HTA submissions for cerliponase alfa for the treatment of for |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | | treatment of CLN2 disease**, which were considered relevant by the EAG**.[36], [37] |
| EAG report, Section 4.2.4, page 72, Table 14 | Change from<br>"*"<br>to<br>"***CLN2 disease affects males and females equally, based on clinical expert opinion**" | The missing Table 14 footnote should be added for clarity and completeness. | Thank you for pointing out the missing table note. The EAG has added it. |
| EAG report, Section 4.2.7.1, page 77 | Change from<br>"i. All patients from pooled studies for cerliponase alfa (i.e., study 190-203, study 190-201/202, and the MAA database and Study 190-901 one-to-one matched patients for SoC."<br>to<br>"i. All patients from ~~**pooled**~~ studies for cerliponase alfa (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." | The phrasing of point 'i' does not clearly reflect which trials were for cerliponase alfa vs SoC. The company suggests rephrasing for clarity. | The EAG have amended the text as suggested by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 4.2.7.1, page 77 | Change from<br>"According to the company, this analysis allows illustrating the impact of delaying treatment initiation."<br>to<br>"According to the company, this analysis **captures the impact of any delay in the full treatment effect of cerliponase alfa being realised (i.e. such that the treatment effect of cerliponase alfa differs between the initial period following treatment initiation and later periods)**." | This analysis relates to any delays in the full treatment effect of cerliponase alfa being realised, rather than any delays in treatment initiation. | The EAG have amended the text as suggested by the company. |
| EAG report, Section 4.2.7.1, page 81 | The EAG considers that the company's preferred evidence source to inform the transition probabilities for those treated with cerliponase alfa introduces considerable uncertainty and potential bias favouring cerliponase alfa into the cost-effectiveness analysis.<br><br>The company would dispute this in terms of baseline distribution across health states. The company therefore suggest that the EAG amend their phrasing to reflect that the baseline distribution across health | The current phrasing used in the EAG report overestimates the uncertainty and bias of the evidence sources, in particular the baseline distribution across health states.<br>The starting score in the clinical studies was liable to the same bias as the MAA with respect to patients potentially having been diagnosed years before study enrolment. Furthermore, studies were conducted across multiple different | Not a factual inaccuracy. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | states was liable to a similar level of bias as MAA participants. | countries, with varying approaches to CLN2 disease referral and diagnosis. | |
| EAG report, Section 4.2.7, page 81 | The EAG reports that "… even a pooled dataset of all clinical trial programme evidence is less affected by delays and interruptions to treatment than the MAA dataset, it may still reflect the population in NHS clinical practice in terms of baseline distribution across health states at treatment initiation."<br><br>The company would like to highlight that the baseline distribution from the clinical trial programmes were also subject to similar delays in diagnosis as the MAA, due to CLN2 diagnosis prior to the availability of cerliponase alfa. Additionally, clinical trials were conducted globally and may reflect the impact of varying healthcare systems and approaches to referral and diagnosis. | The current phrasing may not accurately represent the impact of patient datasets on the baseline distribution. | The EAG has updated the text:<br><br>The EAG notes that even **if** a pooled dataset of all clinical trial programme evidence is less affected by delays and interruptions to treatment than the MAA dataset, it may still **not** reflect the population in NHS clinical practice in terms of baseline distribution across health states at treatment initiation. |
| EAG report, Section 4.2.7.1, Pages 83-84 | "Thus, it is also unknown whether the matching approach allowed balancing the proportion of patients with atypical disease across treatment groups and, if not, what is the likely direction of bias. | The company would like to clarify that the discussion of 3:1 matching is not relevant for the economic model as the matching was done for "all patients" and then sub-grouped. The company note this was not discussed in the CS; | Not a factual inaccuracy. The EAG is clear in the report that the reason why 1:1 rather than 3:1 matching was used is not clear. Furthermore, it is important to note where the comparative clinical evidence reported in the CS differs |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | however, consider it important to highlight this to the EAG for awareness. Please ensure this is made clear in any commentary. | between clinical and economic sections. |
| EAG report, Section 4.2.7.1, page 84 | The company is not sure what the EAG meant by the following sentence and suggests this be rewritten for clarity;<br>"Thus, the EAG cannot comment extensively on the differences in as driven by the evidence used to derive transition probabilities in the original and current appraisal of cerliponase alfa in CLN2." | Clarity | The EAG has amended the text for clarity purposes. The current statement is as follows:<br>"Thus, the EAG cannot comment extensively on the differences in the evidence used to derive transition probabilities in the original and current appraisal of cerliponase alfa in CLN2." |
| EAG report, Section 4.2.7.1, page 85 | Change from"<br>"When study 190-203 was the source of evidence, the specified transition matrix differed from the one used for the 'all patients' dataset by not allowing transitions from ML score 0 to 1 (see Table 32, response to PfCs)"<br>to<br>"When study 190-203 was the source of evidence, the specified transition matrix differed from the one used for the 'all patients' dataset **as no data were available to inform the** transitions from | This structural assumption was only made in the absence of any data to inform this transition. | Not a factual inaccuracy.<br>The EAG has, however, amended the text to clarify that the assumption was made due to the lack of data to inform these transitions. The current text is as follows:<br>"When study 190-203 was the source of evidence, the specified transition matrix differed from the one used for the 'all patients' dataset by not allowing transitions from ML score 0 to 1 due to the |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | ML score 0 to 1 (see Table 32, response to PfCs)“ | | lack of data informing these transitions (see Table 32, response to PfCs).” |
| EAG report, Section 4.2.7.1, page 85 | Change from<br>“For patients treated with cerliponase alfa only transitions between adjacent ML score defined health states (0 to 6) were allowed”<br>to<br>“For patients treated with cerliponase alfa**,** only transitions between adjacent ML score defined health states (**ML score** 0–6; **model health states 1–7, and MSM model 0–6**) were allowed” | The missing number definition in the brackets may lead to confusion. Addition of definition is recommended for clarity. | The EAG has amended the text as suggested by the company for the clarity purposes. |
| EAG report, Section 4.2.7.1, page 86 | The company suggests the EAG amend the following:<br>“B2.e) may suggest overfitting of the models in some health states appears to not fit well for others, particularly for the cerliponase alfa-treatment group” | This sentence appears to be unsuitably written and is currently difficult to interpret. The company suggest the EAG report text is amended to provide additional clarification. | The EAG has amended the text. The current text is as follows:<br>“The estimated **models’ goodness-of-fit,** as illustrated by a comparison between expected and observed health state prevalence (see response to clarification question B2.e), may suggest overfitting **of the predicted model outputs to the observed data in some health states, while in other health states the fit appears to be** |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | | **poor. This is** particularly **the case** for the cerliponase alfa-treatment group (see Figure 12 and Figure 13)." |
| EAG report, Section 4.2.7.2, page 88 | Change from<br>"Transitions beyond health state 7 are independent of treatment group, and once patients reach health state 8 disease improvement is no longer possible (see Table, 44, CS). The company considers that in the absence of comparative evidence between cerliponase alfa and the SoC, this is a conservative assumption"<br>to<br>"Transitions beyond health state 7 are independent of treatment group; **the company considers that in the absence of comparative evidence between cerliponase alfa and the SoC, this is a conservative assumption. Once patients reach health state 8 disease improvement is no longer possible** (see Table, 44, CS)" | The company's assessment that the assumption is conservative only relates to the first part of the previous sentence. | Not a factual inaccuracy.<br>The EAG has amended the text for clarity purposes. The updated text is as follows:<br>"Transitions beyond health state 7 are independent of treatment group, **which the company considers a conservative assumption in the absence of comparative evidence between cerliponase alfa and SoC**. Once patients reach health state 8 disease improvement is no longer possible (see Table, 44, CS)." |
| EAG report, Section 4.2.7.2, page 89 | Change from | In the model, the mean *undiscounted* time in health state 6 is 3.2 years. | EAG has accepted the amendment to correct the statement. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "In the company's base case, mean time (discounted) in health state 6 corresponds to 3.2 years"<br>to<br>"In the company's base case, mean time (**undiscounted**) in health state 6 corresponds to 3.2 years" | | |
| EAG report, Section 4.2.7.2, page 92 | Change from<br>"Furthermore, the proportion of patients with vision loss was assumed to increase linearly from 0% at age 6 to 100% at age 20 years old"<br>to<br>"Furthermore, the proportion of patients with vision loss was assumed to increase linearly from 0% at age 6 to 100% at age 20 years old i**n health states 1–6**" | This approach to modelling vision loss is only applied in health states 1–6. | The EAG has accepted the amendment as suggested by the company. |
| EAG report, Section 4.2.7.4, page 93 | The EAG considers that the original HST12 approach to modelling vision loss is more appropriate than the company's, given that the clinical evidence submitted by the company did not suggest that cerliponase alfa improves or stabilises vision loss.<br>However, the company notes that the EAG acknowledges the clinical evidence | The clinical evidence outlined in the CS suggests a delay in vision loss, a point acknowledged in the EAG's assessment of the clinical data (EAG report, Section 3.3.3, page 44). Consequently, it seems fitting to model the onset of vision | The EAG has amended the report as follows:<br>"the clinical evidence submitted by the company did not suggest that cerliponase alfa improves or stabilises vision loss **in the long-term as acknowledged by the company (see Section 3.4.2).** |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | presented in the CS suggests a delay to vision loss is associated with cerliponase alfa treatment. The company therefore suggests the EAG report be amended to note that the company's approach to modelling vision loss is appropriate and aligned with the presented clinical evidence. | loss at a later age in patients treated with cerliponase alfa. | **The EAG, notes, however, that short-term clinical evidence presented in Section 3.3.3, suggests that vision may be preserved for a time, with little vision loss in the first three years of treatment. However, vison appears to be lost rapidly, thereafter."** |
| EAG report, Section 4.2.7.5, page 94 | Change from<br>"The assumption that patients experience general population mortality does not seem unreasonable to the EAG"<br>to<br>"The assumption that patients experience general population mortality **in health states 1–8** does not seem unreasonable to the EAG" | Only patients in health states 1–8 are assumed to experience general population mortality. | The EAG has accepted the amendment as suggested by the company. |
| EAG report, Section 4.2.8, page 97 | The EAG report that "In the original HST12, treatment discontinuation was assumed to occur at health state 7. The company has not justified why they have chosen to deviate from the previous assumption on treatment discontinuation."<br>The company would like to highlight that this statement is contradictory to clinical | Evidence provided by the EAG clinical expert may support assumptions in the CS. | This is not a factual inaccuracy.<br>The EAG noted that according to clinical opinion there is variability in clinical practice in terms of stopping rules, but also that the current model implementation of |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | opinion reported on page 96 of the EAG report, where it is stated that "…families might prefer to continue treatment while a benefit on quality of life was maintained (particularly due to seizure control), while other might consider treatment discontinuation as early as health state 5 (ML score 2)". Given this, discontinuation at health state 6 (ML score 1) could be considered a midpoint between discontinuation at health state 5 (ML score 2) and the committee preferred assumptions in HST12 of discontinuation at health state 7 (ML score 0). | | the discontinuation rule implies a maintenance of treatment effect after cerliponase alfa discontinuation on health state 6 permanence and that patients can restart cerliponase alfa treatment after discontinuation. |
| EAG report, Section 4.2.10, page 101 | The EAG note that "…the company stated that they excluded one patient from the analysis of MAA utilities because that person's utility value was assessed as implausibly high for a patient with ML score of 0 (exact value not provided). It is unclear whether this refers to a single or multiple observations."<br><br>The company would like the highlight that there was an error identified in the MAA database which was subsequently corrected by the company prior to analysis included in the CS. | Company clarification | Not an EAG factual inaccuracy, but the EAG has removed the sentence, as the company states the issue was fixed. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | The company has reviewed the text presented in the CS in a footnote to Table 53, page 144 "†Note that one patient was excluded from the analysis as implausibly high utility values were recorded for a patient with ML score of 0.". This sentence should be omitted. | | |
| EAG report, Section 4.2.11.5, page 111 | Please complete the following sentence:<br>"While the frequency of replacement assumed in the company's model is aligned with the recommendations of cerliponase alfa's SmPC." | The sentence appears to be incomplete. | Thank you for indicating this typo. The EAG has amended the text to correct it. The current text is as follows:<br>"The EAG notes that it is unclear whether the costs of replacing the ICV device have been under or overestimated by the company. **The EAG further notes that** the frequency of replacement assumed in the company's model is aligned with the recommendations of cerliponase alfa's SmPC." |
| EAG report, Section 4.2.11.9, page 114 | Change from<br>"The company applied the costs associated with vision loss to i) all patients in health states 7-9 and ii) a proportion of patients in | Vision loss in health states 1 to 6 was not assumed before the age of 6. | The EAG has amended the text as suggested by the company for the clarity purposes. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | health states 1-6, which rose linearly from 0 to 100% at age 20”<br><br>to<br><br>“The company applied the costs associated with vision loss to i) all patients in health states 7–9 and ii) a proportion of patients in health states 1–6, which rose linearly from 0 **at age 6** to 100% at age 20” | | |
| EAG report, Section 6.1.1.8, Page 130 | The EAG base case includes the cost of ECG to the infusion costs of cerliponase alfa, in line with the recommendation in the SmPC.<br><br>The company would like to highlight that the cost of a cardiologist, included in the company submission and economic model, should be removed to avoid double counting the costs associated with ECGs.<br><br>Moreover, the company would recommend that this assumption is validated with a clinical expert that the “clinically significant ECG-12 abnormalities” (page 130, EAG report) reported in the MAA are those that require monitoring using an ECG at every infusion, as specified in the SmPC. | The EAG scenario may not accurately reflect clinical practice. | This is not a factual inaccuracy. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 6.1.1.10, page 131 | The company would like to highlight that the inclusion of scenario 11 (including psychiatric/behavioural support costs) contradicts clinical advice received by the company and suggests that this scenario be removed. | This scenario contradicts clinical advice received by the company. | This is not a factual inaccuracy. |

**Issue 2 Factual inaccuracies**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 2.2.5, page 29 | Change from<br>"Currently, there are six centres in the UK…."<br>to<br>"Currently, there are six centres in **England**…." | The six listed centres are all in England. | This has been amended in section 2.2.3, page 29. |
| EAG report, Section 2.3.4, page 34 | Change<br>"The CS did not report any subgroup analyses. The EAG considers that subgroup analyses based on age and ML score at treatment initiation may have been helpful but would have limited statistical power."<br>to<br>"**The CS included subgroup analyses by stage of progression, specifically time to disease manifestation analysis of participants in Study 190-203 with MLVS score of 12 (in Document B, Section B.2.6.3.5). The CS also included an analysis of outcomes in 190-203 participants based on age at baseline (Appendix O, Section O.3.3.).**<br>**Furthermore, in response to the EAG's clarification questions A3 and A4, the** | The EAG considered that no subgroup analyses were performed. The company flags that subgroup analyses based on age and ML score were provided for study 190-203 and were therefore available for critique by the EAG. Subgroup analysis of outcomes in 190-203 participants based on age at baseline were also included. The company acknowledges that data for these subgroups were not available from Study 190-201/202, the MAA, DEM-CHILD-RX, or Study 190-801.<br>In response to the EAG's clarification questions A3 and A4, the company included a subgroup analysis of progression based on baseline MLVS score, and baseline scores for the four | We have made some changes to Table 2 and section 2.3.4, but different from those suggested |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | **company included a subgroup analysis of progression. The analyses included the tabulation of numbers and percentages of patients experiencing an unreversed 1-point, 2-point, 3-point etc. decline M, L, V, S, ML, and MLVS score from baseline at each year of follow-up for participants pooled across 190-201/202, 190-203, and the MAA.** ” | components (motor, language, vision, seizures) separately. | |
| EAG report, Section 3.2.1, page 37, Table 3 | Change weeks of follow-up for Study 190-201/202 from “239” to “**280**” | The last dosing visit for 190-201/202 combined was at Week 280 (range 0.1–300 weeks). This reflects 48 weeks of follow-up for 190-201, followed by 240 weeks for 190-202, followed by 24 weeks of safety follow-up (on commercial drug). As 190-201 had a dose escalation phase, some patients experienced longer follow-up and received treatment for longer than 280 weeks (maximum follow-up was 300 weeks). | This has been amended in section 3.2.1. |
| EAG report, Section 3.2.1, page 39 | Change from<br>“In the analysis pooling all studies, requested by the EAG at time of clarification, a 1:1 matching was used.”<br>to | For accuracy this sentence should be amended, as the pooled matched analysis was conducted prior to the EAG’s clarification questions, during the development of the company’s economic model. | This is not a factual inaccuracy. However, we have changed “requested by” to “given to” in section 3.2.1.3 for clarity. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | “In the analysis pooling all studies, ~~**requested by the EAG at time of clarification, a**~~ 1:1 matching was used | | |

<table>
<tr>
<td>EAG report, Section 3.2.1, page 39, Table 4</td>
<td>Change Table 4 from
<table>
<tr><th>MSA</th><th>Studies in CS</th><th>Sample size</th><th>Weeks of follow-up</th><th>Mean age* (SD)</th><th>Mean ML score* (SD)</th><th>% with ML score=6* (n)</th><th>Sex % female</th></tr>
<tr><td rowspan="2">1</td><td>109-201/202</td><td>17</td><td>239</td><td>4.6 (0.74)</td><td>3.40 (1.33)</td><td>12 (2)</td><td>65</td></tr>
<tr><td>190-901</td><td>17</td><td></td><td>4.6 (0.72)</td><td>3.40 (1.33)</td><td>12 (2)</td><td>41</td></tr>
<tr><td rowspan="2">2</td><td>190-203</td><td>12</td><td>169</td><td>2.7 (1.12)</td><td>5.0 (1.41)</td><td>NR</td><td>66.7</td></tr>
<tr><td>190-901</td><td>29</td><td></td><td>2.7 (1.09)</td><td>5.0 (1.38)</td><td>NR</td><td>52.8</td></tr>
<tr><td rowspan="2">3</td><td>MAA cohort FAS</td><td>26</td><td>209</td><td>4.37 (1.07)</td><td>4 (1.26)</td><td>11.54 (3)</td><td>23</td></tr>
<tr><td>190-901</td><td>26</td><td></td><td>4.35 (1.11)</td><td>4 (1.26)</td><td>11.54 (3)</td><td>50</td></tr>
<tr><td rowspan="2">4</td><td>MAA Cohort ex-trial</td><td>17</td><td>209</td><td>4.56(1.10)</td><td>4.12 (1.11)</td><td>0</td><td>0</td></tr>
<tr><td>190-901</td><td>17</td><td></td><td>4.53 (1.18)</td><td>4.12 (1.11)</td><td>0</td><td>53</td></tr>
<tr><td rowspan="2">5</td><td>DEM-CHILD-RX</td><td>21</td><td>26†</td><td>4.7 (1.94)</td><td>3.90 (1.58)</td><td>24 (5)</td><td>52</td></tr>
<tr><td>DEM-CHI</td><td>21</td><td></td><td>4.7 (1.92)</td><td>3.90 (1.58)</td><td>24 (5)</td><td>24</td></tr>
</table>
</td>
<td>To accurately reflect what is stated in the CS, Document B, Section 2.6.<br><br>Several inaccuracies were identified in Table 4, including the weeks of follow-up for 190-202.<br><br>Data for participants in 190-203 with % ML score of 6 were not reported in the CS, but were available in the CSR, Table 14.2.4.4.<br><br>The MAA new starter cohort, not the ex-trial cohort, was matched in the CS.<br><br>As information on participant sex was not collected during the MAA, the % female was unknown in participants in the MAA new starter cohort. To prevent the data being misleading, a table footnote should be included detailing how the MAA data was collected.</td>
<td>The table has been amended.</td>
</tr>
</table>

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | LD-NH | | | | | | |

*At baseline, †Participant follow-up was started at different timepoints, duration of follow-up therefore varied for patients (minimum follow-up was 6 months); MSA is matched study group; FAS is full analysis set.

to

| **MSA** | **Studies in CS** | **Sample size** | **Weeks of follow-up** | **Mean age* (SD)** | **Mean ML score* (SD)** | **% with ML score=6* (n)** | **Sex % female** |
|---|---|---|---|---|---|---|---|
| 1 | 190-201/202 | 17 | **280** | 4.6 (0.74) | 3.40 (1.33) | 12 (2) | 65 |
| | 190-901 | 17 | | 4.6 (0.72) | 3.40 (1.33) | 12 (2) | 41 |
| 2 | 190-203 | 12 | 169 | 2.7 (1.12) | 5.0 (1.41) | **58 (7)** | 66.7 |
| | 190-901 | 29 | | 2.7 (1.09) | 5.0 (1.38) | **62 (18)** | 52.8 |
| 3 | MAA cohort FAS | 26 | 209 | 4.37 (1.07) | 4 (1.26) | 11.54 (3) | 23¶ |
| | 190-901 | 26 | | 4.35 (1.11) | 4 (1.26) | 11.54 (3) | 50 |
| 4 | MAA Cohort **new starter** | 17 | 209 | 4.56(1.10) | 4.12 (1.11) | 11.8 (2) | **NA¶** |
| | 190-901 | 17 | | 4.53 (1.18) | 4.12 (1.11) | 11.8 (2) | 53 |
| 5 | DEM- | 21 | 26† | 4.7 (1.94) | 3.90 (1.58) | 24 (5) | 52 |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | CHIL D-RX | | | | | | | |<br>DEM - CHIL D-NH | 21 | | 4.7 (1.92) | 3.90 (1.58) | 24 (5) | 24<br>*At baseline, †Participant follow-up was started at different timepoints, duration of follow-up therefore varied for patients (minimum follow-up was 6 months); **¶Sex not collected as part of MAA, therefore sex % female of participants in MAA new starter cohort is 100% unknown.** MSA is matched study group; FAS is full analysis set. | | |
| EAG report, Section 3.2.2., page 39–40 | Change from<br>"The primary outcome measured by the company was a responder analysis on the 6-point adapted CLN2 ML scale which included two assessments: rate of decline and time to unreversed two-point decline or score of zero in CLN2 scores by week W48. The time from baseline to first unreversed decline in CLN2 ML score and time from baseline to first unreversed two-point decline or total score of zero were summarised using the Kaplan Meier estimates and Cox proportional hazards model." | To reflect the evidence submitted within the CS. | This has been amended in section 3.2.2. |

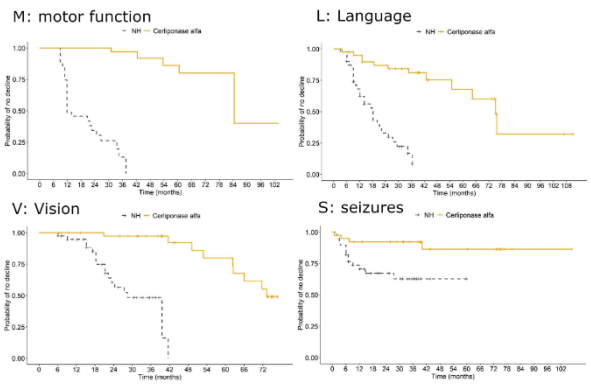
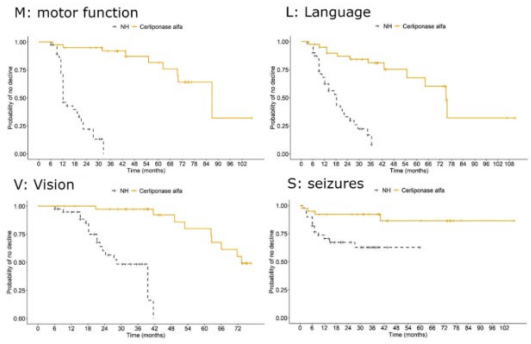
| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | to<br>"The primary outcome measured by the company was a responder analysis on the 6-point adapted CLN2 ML scale which included **three** assessments: rate of decline, time to unreversed two-point decline or score of zero in CLN2 scores by week W48**, and time to ML score of zero.** ~~**The time from baseline to first unreversed decline in CLN2 ML score and**~~ **T**ime from baseline to first unreversed two-point decline or ~~**total**~~ score of zero **and time to ML score of zero, were** summarised using the Kaplan Meier estimates and Cox proportional hazards model." | | |
| EAG report, Section 3.3.1, page 41 | Change from<br>"Median time to a 2-point decline with cerliponase alfa was around four years."<br>to<br>"Median time to a 2-point decline with cerliponase alfa was around four **and a half** years." | Median time to a 2-point decline with cerliponase alfa is 4.575, therefore four and a half years is more accurate. | This has been amended in Section 3.31 |
| EAG report, Section 3.3.1, page 41 | Change from<br>"Natural history patients had a rate of decline of 1.36 points every 48 weeks." | To accurately reflect what is stated in the company clarification question A3 response, page 10. | This typo has been corrected in Section 3.31 |

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td>to<br><br>“Natural history patients had a rate of decline of 1.26 points every 48 weeks.”</td><td></td><td></td></tr>
<tr><td>EAG report, Section 3.3.1, page 41</td><td>Change from<br><br>“The rate of decline with cerliponase alfa also varied across the three main sources of evidence: it was 0.53 points per 48 weeks in 190-202”<br><br>to<br><br>“The rate of decline with cerliponase alfa also varied across the three main sources of evidence: it was 0.42 points per 48 weeks in 190-202”</td><td>To accurately reflect what is stated in the CS (Document B, Sections B2.6.2.2).<br><br>Although a rate of 0.52 points per 48 weeks was reported in 190-202, this was an interim analysis after 48 weeks of follow-up.<br><br>At the end of the evaluation period, the rate of decline for cerliponase alfa treated participants in Study 190-202 decreased to 0.42 points per 48 weeks.</td><td>This has been corrected in Section 3.31</td></tr>
<tr><td>EAG report, Section 3.3.1, page 42, Table 5</td><td>Change Table 5 from<br><table><tr><th>Study</th><th>Decline in ML score (points per 48 weeks)</th><th>Hazard ration for unreversed 2-point decline in ML score</th></tr><tr><td>190-202</td><td>0.53 (95% CI: 0.20 to 0.86)</td><td>0.06 (95% CI: 0.02 to 0.25)</td></tr><tr><td>190-203</td><td>0.15 (95% CI: 0 to 0.30)</td><td>0.091 (95% CI: 0.021 to 0.393)</td></tr><tr><td>MAA cohort</td><td>0.23 (95% CI: -0.03 to 0.50)</td><td>0.126 (95% CI: 0.05 to 0.31)</td></tr></table>To</td><td>To accurately reflect what is stated in the CS (Document B, Sections B2.6.2.2 and B2.6.4.2, respectively):<ul><li>At the end of the evaluation period, the rate of decline for cerliponase alfa treated participants in Study 190-202 was 0.42 points per 48 weeks</li><li>The rate of decline stated for the MAA study is specifically for the full analysis set (FAS).</li></ul></td><td>This has been corrected in Section 3.31, Table 5</td></tr>
</table>

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td>
<table>
<tr><th>Study</th><th>Decline in ML score (points per 48 weeks)</th><th>Hazard ration for unreversed 2-point decline in ML score</th></tr>
<tr><td>190-202</td><td>0.42 (95% CI: 0.12 to 0.71)</td><td>0.06 (95% CI: 0.02 to 0.25)</td></tr>
<tr><td>190-203</td><td>0.15 (95% CI: 0.00 to 0.30)</td><td>0.091 (95% CI: 0.021 to 0.393)</td></tr>
<tr><td>MAA FAS cohort</td><td>0.23 (95% CI: -0.03 to 0.50)</td><td>0.126 (95% CI: 0.05 to 0.31)</td></tr>
</table>
</td><td>• Correction of the number of decimal places</td><td></td></tr>
<tr><td>EAG report, Section 3.3.1, page 42</td><td>Change from<br>“….natural history patients (HR 0.06, 95% CI 0.2 to 0.25)”<br>to<br>“….natural history patients (HR 0.06, 95% CI 0.02 to 0.25)”</td><td>Correction of lower 95% confidence interval.</td><td>This typo has been corrected in Section 3.31</td></tr>
<tr><td>EAG report, Section 3.3.2, page 42</td><td>Change from<br>“The 190-202 trial also had a faster rate of decline in ML score of 0.53 points per 48 weeks (or 1 point every 2 years). This</td><td>To accurately reflect what is stated in the CS (Document B, Sections B2.6.2.2).<br>At the end of the evaluation period, the rate of decline for cerliponase alfa</td><td>This typo has been corrected in Section 3.32 and the text slightly amended for clarity.</td></tr>
</table>

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | suggests that the rate of decline in ML score may increase after approximately 3 years."<br><br>to<br><br>"The 190-202 trial also had a faster rate of decline in ML score of **0.42** points per 48 weeks (or 1 point every **2.4** years). ~~**This suggests that the rate of decline in ML score may increase after approximately 3 years**~~." | treated participants in Study 190-202 was 0.42 points per 48 weeks.<br><br>It is not clear where the EAG derived the prediction of an increase after 3 years, the company suggests that this be removed. | |
| EAG report, Section 3.3.1, page 44 | Change from<br><br>"When examining time to an MLVS score of zero, more than half of the natural history patients had declined to a score of zero within about four years."<br><br>to<br><br>**"An MLVS score of zero was reported for five natural history patients within approximately four years**" | For accuracy, this sentence should be amended, as the proportion reported by the EAG does not take into consideration patient censoring at the end of follow-up. | The EAG thinks it appropriate to draw conclusions from Kaplan-Meier curves, even with censoring. Some amendments have been made for this and subsequent points to clarify this. |
| EAG report, Section 3.3.1, page 44 | Change from<br><br>"For the motor and language subscales all natural history patients had declined by at least two points within three years."<br><br>to | To accurately reflect the analysis conducted by the company; the EAG has not accounted for participant censoring in their interpretation of the data | See point above and edits to section 3.3.1 |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "For the motor and language subscales all natural history patients had **either** declined by at least two points within three years **or were censored at the end of follow-up**." | | |
| EAG report, Section 3.3.1, page 44 | Change from<br>"For motor function only around 25% of patients experience a two-point decline within 5-6 years. Language appears to be lost faster, with around half of patients having lost two-points within 5-6 years."<br>to<br>"For motor function ~~**only around 25%**~~ **7%** of patients experience a two-point decline within 5–6 years. ~~**Language appears to be lost faster, with around half of patients having**~~ 11/40 participants lost two-points on the language scale up to 6.3 years." | To accurately reflect the analysis conducted by the company; the EAG has not accounted for participant censoring in their interpretation of the data | See point above and edits to section 3.3.1 |
| EAG report, Section 3.3.1, page 45, Figure 5 | Change Figure 5 from | The figure generated by the EAG was not accurate as the motor score Kaplan-Meier represented time to score of zero for motor function, instead of time to unreversed 2-point decline in M score. | This figure has been replaced with a correct version |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| |  <br>to<br>  | | |
| EAG report, Section 3.3.3, page 46 | Change from<br>“The EAG notes that the predicted rate of decline is slower for language than motor function in Table 7, but this is the opposite of | The rate of decline takes into account the entire follow-up. Therefore, the initial plateau observed for motor | This paragraph has been deleted. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | what was observed from Kaplan-Meier curves in Figure 5, where language appears to decline faster."<br>to<br>**"The EAG notes that the predicted rate of decline is slower for language than motor function in Table 7, but this is the opposite of what was observed from Kaplan-Meier curves in Figure 5, where language appears to decline faster."** | function would not imply a slower rate of decline. | |
| EAG report, Section 3.4.6, page 49 | Change from<br>"In the MAA cohort mean myoclonus scores…."<br>to<br>"In the MAA **new patient** cohort mean myoclonus scores…." | For accuracy it should be mentioned that this outcome was reported for the MAA new patient cohort only. | Amended |
| EAG report, Section 3.4.7, page 49 | Change from<br>"Also, in study 201/202 there was a protocol amendment in which EQ-5D-5L assessments were removed…."<br>to<br>"Also, **both studies 190-201/202 and 190-203 had** protocol amendment**s** in which EQ-5D-5L assessments were removed…." | The protocol amendment removing the assessment of EQ-5D-5L, was performed for both studies 190-201/202 and 190-203.<br>The resulting short time for data collection resulted in insubstantial data for this outcome, which is why it was not included in the CS. | Amended |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 3.5.1, page 51–52 | Change from<br>"The company's advisers thought that the rate of ICV infusions that lead to infection would be significantly lower in clinical practice."<br>to<br>"The company's advisers **were confident** that **the incidence of infections per ICV infusion** would be significantly lower in clinical practice." | The EAG wording used in this sentence suggests that the advisers were guessing that the rate would be significantly lower. The company suggests amending this sentence, in order to better reflect the advisers' conclusion. | Not a factual inaccuracy. |
| EAG report, Section 3.5.1, page 52 | Change from<br>"They found rates for device-related malfunctions were 0.27% and device-related infections were 0.33%"<br>to<br>"They found rates for device-related **adverse events** were 0.27% and device-related infections were 0.33%" | Correction of the outcome to reflect what was reported in the Schwering et al 2021 study, referenced by the EAG. | Amended |
| EAG report, Section 3.5.2, page 52 | Change from<br>"For the clinical trials, in study 202, 22 of the 24 patients had baseline ECGs, of which four were abnormal (but not clinically significant). In study 203, 6 of the 14 patients (43%) had an ECG abnormality at baseline (none were | According to Table 14.3.7.3 in the CSR, the number of ECG abnormalities at baseline for participants in Study 190-203 was seven. | Our reading of this table is 6 abnormalities at baseline and 7 at last visit.<br>Full study names added. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | deemed clinically significant). During the trials ECG abnormalities were more frequent in study 201/202 than in study 203. Seven patients (29%) experienced 15 cardiovascular and ECG AEs in the study 190-201/202 cohort, all of which were grade 1 or 2 events. In study 203, three participants experienced 4 cardiovascular AEs, which included one ECG abnormality."<br><br>to<br><br>"For the clinical trials, in study **190-202**, 22 of the 24 patients had baseline ECGs, of which four were abnormal (but not clinically significant). In study **190-203, 7** of the 14 patients (43%) had an ECG abnormality at baseline (none were deemed clinically significant). ~~**During the trials ECG abnormalities were more frequent in study 201/202 than in study 203.**~~ Seven patients (29%) experienced 15 cardiovascular and ECG AEs in the study **190-201/202** cohort, all of which were grade 1 or 2 events. In study **190-203**, three participants experienced 4 cardiovascular AEs, which included one ECG abnormality." | For consistency with the rest of the EAG report, the full study name should be used.<br><br>Study 190-201/202 had a much longer follow-up compared with Study 190-203, therefore the frequency of EAG abnormalities is not considered directly comparable. | |
| EAG report, Section 3.9, page 58 | Change from | To accurately reflect the analysis conducted by the company; the EAG has not accounted for participant | Change made as suggested |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "All patients declined by at least two points on the CLN2 ML scale within three years."<br>to<br>"All patients declined by at least two points on the CLN2 ML scale within three years**, or were censored.**" | censoring in their interpretation of the data. | |
| EAG report, Section 3.9, page 58 | Change from<br>"Only around half of patients had a decline of two or more points on the CLN2-ML scale within 5 years, and very few had a decline to a score of zero. The data suggest a typical rate of decline in ML score might be around 1 point of decline every 3 or 4 years., with about a 1 point decline every 6 years in both motor function and language."<br>to<br>"**Of the participants that were uncensored at the end of follow-up, only** around half ~~**of patients**~~ had a decline of two or more points on the CLN2-ML scale within 5 years, and very few had a decline to a score of zero. The data suggest a typical rate of decline in ML score might be around 1 point of decline every 3 or 4 years.~~**, with about a 1 point decline every 6 years in both motor function and language**~~." | To accurately reflect the analysis conducted by the company; the EAG has not accounted for participant censoring in their interpretation of the data.<br>The latter part of the second sentence does not support the start of the sentence and should be removed for clarity. | Sentence edited to clarify it is based on Kaplan-Meier analyses. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 3.9.1, page 60 | Change from<br>"Disease progression after long-term use of cerliponase alfa is currently unclear because trials have not yet extended beyond five years of follow-up."<br>to<br>"Disease progression after long-term use of cerliponase alfa **has been shown over 5 years in trials and up to a maximum of 9.5 years in MAA ex-trial participants; CLN2 disease progression with cerliponase alfa beyond this is unclear**." | To accurately reflect the length of cerliponase alfa treatment use in the evidence base. | Section 3.9.1 edited to explicitly name the trials. |
| EAG report, Section 4.1, page 62 | Change from<br>"…..has completed its follow-up (239 weeks on study)"<br>to<br>"…..has completed its follow-up (**280** weeks on study)" | The last dosing visit for 190-201/202 combined was at Week 280 (range 0.1–300 weeks). This reflects 48 weeks of follow-up for 190-201, followed by 240 weeks for 190-202, followed by 24 weeks of safety follow-up (on commercial drug). As 190-201 had a dose escalation phase, some patients experienced longer follow-up and received treatment for longer than 280 weeks (maximum follow-up was 300 weeks). | The EAG has accepted the amendment. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 4.1, page 62 | Change from<br>"….and new starters in the NHS (72 weeks follow-up)"<br>to<br>"….and new starters in the NHS (**209** weeks follow-up)" | Correction of the number of weeks of follow-up | The EAG has accepted the amendment. |
| EAG report, Section 4.2.7, page 76 | Change from<br>"The company assumed that the proportion of patients who enter the model in health state 1 (ML score 6) are initial stabilisers and all remain in health state 1 (unless they die or discontinue treatment)"<br>to<br>"The company assumed that the proportion of patients who enter the model in health state 1 (ML score 6) are initial stabilisers and all remain in health state 1 (unless they die ~~**or discontinue treatment**~~)" | In the model, patients do not discontinue treatment in health state 1. | The EAG has accepted the amendment. |
| EAG report, Section 4.2.7.1, page 79, Table 16 | Change from<br>"6.1%"<br>to | Correction of percentage value | The EAG has accepted the amendment. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | **"0.7%"** in Table 16, column "Piecewise at 6 months – 'all patients'; non-stabilisers <6 month", row "ML score 6 to 5" | | |
| EAG report, Section 4.2.7.1, page 81 | Change from<br>"….full follow-up of Study 190-201/202 (n=22 matched patients)…."<br>to<br>"….full follow-up of Study 190-201/202 **(15 of the 40 matched cerliponase alfa treated participants. Of the 15, 2 had additional follow-up in the MAA)**…." | The number of participants listed was inaccurate | The EAG has accepted the amendment. |
| EAG report, Section 4.2.7.1, page 89 | Change from<br>"In the company's base case, mean time (discounted) in health state 6 corresponds to 3.2 years…"<br>to<br>"In the company's base case, mean time (**half-cycle corrected**) in health state 6 corresponds to 3.2 years…" | Correction of wording to reflect methods | The EAG has amended the text. The current text is as follows:<br>"In the company's base case, mean time (**undiscounted and half-cycle corrected**) in health state 6 corresponds to 3.2 years" |
| EAG report, Section 4.2.10.3, page 104 | Change from<br>"The company did not provide more detailed new information on the PedsQL data and did | Additional explanation of company response to EAG clarification questions was missing. | The EAG does not consider this statement a factual inaccuracy. The explanation provided by the company is available in the |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | not conduct the requested scenario analysis."<br><br>to<br><br>"The company did not provide more detailed new information on the PedsQL data and did not conduct the requested scenario analysis. T**he company did not consider this analysis to be informative, for the following reasons:**<br><br>• **All studies that collected PedsQL also collected EQ-5D data**<br>• **HRQoL data would not be available for SoC or for the health states associated with the lowest ML scores**<br>• **A limited number of mapping studies in relevant patient populations are available**." | | response to the points of clarification letter. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 4.2.11.1, page 107 | Please remove the following statement:<br>"The EAG notes that there are confidential commercial arrangements in place for drugs comprising the comparator regimen or subsequent treatments" | In the model, cerliponase alfa is not compared with any active treatments, and no subsequent therapies are considered. | The EAG has amended the text, as follows:<br>"The EAG notes that there are **no** confidential commercial arrangements in place for drugs comprising the comparator regimen or subsequent treatments." |
| EAG report, Section 4.2.11, page 113 | Change from<br>"Secondly, in the vignettes feeding tubes are assumed to be required from health state 3 onwards"<br>to<br>"Secondly, in the vignettes feeding tubes are assumed to be required from health state **4** onwards." | In the utility study vignettes, feeding tubes are assumed to be required for cerliponase alfa patients from health state 4 onwards | The EAG has amended the text to correct the statement. The current text is as follows:<br>"Secondly, in the vignettes feeding tubes are assumed to be required from health state 2 onward for SoC and from health state 4 onwards for cerliponase alfa treatment group. However, in the company's model, the proportion of patients requiring a feeding tube in the cerliponase alfa treatment group is 0% in health states 1-4 and only 20% of these patients require a feeding tube in health state 5 (see Table 19)." |
| EAG report, Section 6.1.1.2, page 128 | Change from<br>"In scenario 3.2 the EAG assumes 75% of the non-stabilisers rate of progression (25% | Correction to statement | The EAG has accepted the amendment as suggested by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | progression multiplier) applied to estimate the transition probabilities of initial stabilisers”<br>to<br>“In scenario 3.2 the EAG assumes 75% of the non-stabilisers rate of progression (25% progression **reduction**) applied to estimate the transition probabilities of initial stabilisers” | | |
| EAG report, Section 6.5, page 145 | Change<br>“…..has completed its follow-up (239 weeks on study )”<br>to<br>“…..has completed its follow-up (280 weeks on study )” | The last dosing visit for 190-201/202 combined was at Week 280 (range 0.1–300 weeks). This reflects 48 weeks of follow-up for 190-201, followed by 240 weeks for 190-202, followed by 24 weeks of safety follow-up (on commercial drug). As 190-201 had a dose escalation phase, some patients experienced longer follow-up and received treatment for longer than 280 weeks (maximum follow-up was 300 weeks). | The EAG has accepted the amendment as suggested by the company. |

### Issue 3 Typographical errors

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| The company has identified a number of typographical and grammatical errors within the EAG report. However, these errors have only been noted in this table in instances where the company consider them to be factual inaccuracies or where the error may alter the intended meaning. | | | |
| The spelling of cerliponase alfa | The company request that the EAG ensure the correct spelling of cerliponase alfa has been used throughout the report. The company has noted that “cerliponase” only and “cerliponase alpha” have been used in several instances. | Correction of treatment name | Corrected |
| EAG report, Section 1.1, page 12 | Change from<br>“Delaying disease progression and indirectly leading life expectancy extension;”<br>to<br>“Delaying disease progression and indirectly leading **to** life expectancy extension” | Clarity | Amended |
| EAG report, Section 1.2 | Points 7 and 8 are duplicated | Correction of duplicated point | Amended |
| EAG report, Section 1.5, page 19 | Change from<br>“….initial stabilisation assumption for patients treated cerliponase is highly uncertain”<br>to | Clarity | Amended |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "….initial stabilisation assumption for patients treated **with** cerliponase **alfa** is highly uncertain" | | |
| EAG report, Section 1.5, page 23 | Change from<br>"….implies a persistence of treatment effect of cerliponase alfa on transition probabilities from health state 6 that potentially too optimist according to clinical advice received by the EAG"<br>to<br>"…. implies a persistence of treatment effect of cerliponase alfa on transition probabilities from health state 6 that **is** potentially too **optimistic** according to clinical advice received by the EAG" | Clarity | Amended |
| EAG report, Section 2.1, page 26 | Change from<br>"which is an extension of study 190/201"<br>to<br>"which is an extension of study **190-201**" | Correction of study name | Corrected |
| EAG report, Section 3.3.1, page 42 | Change from<br>"….ML score in trial 192-202 is shown in Figure 3"<br>to | Correction of study name | Corrected |

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td>“….ML score in trial 190-202 is shown in Figure 3”</td><td></td><td></td></tr>
<tr><td>EAG report, Section 3.3.2, page 43</td><td>Change from<br>“ …. .0.17 (95% CI 0.089 to 0.322)”<br>to<br>“…. .0.170 (95% CI 0.089 to 0.322).”</td><td>Correction of the number of decimal places</td><td>No change (2dp preferred)</td></tr>
<tr><td>EAG report, Section 3.3.3, page 44</td><td>Change from<br>“….Very few patents on cerliponase alfa”<br>to<br>“….Very few patients on cerliponase alfa”</td><td>Correction of spelling</td><td>Corrected</td></tr>
<tr><td>EAG report, Section 3.3.3, page 46</td><td>Change from
<table>
<tr><th>Subscale</th><th colspan="2">Mean rate of decline (points per 48 weeks, with SD)</th></tr>
<tr><th></th><th>Natural history</th><th>Cerliponase alfa</th></tr>
<tr><td>Motor</td><td>0.69 (0.48)</td><td>0.19 (0.56)</td></tr>
<tr><td>Language</td><td>0.58 (0.49)</td><td>0.13 (0.17)</td></tr>
<tr><td>Vision</td><td>0.55 (0.46)</td><td>0.23 (0.28)</td></tr>
<tr><td>Seizures</td><td>0.2 (0.62)</td><td>-0.17 (0.49)</td></tr>
</table></td><td>Correction of the number of decimal places</td><td>Corrected</td></tr>
</table>

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td>To<br><br><table><tr><th>Subscale</th><th colspan="2">Mean rate of decline (points per 48 weeks, with SD)</th></tr><tr><th></th><th>Natural history</th><th>Cerliponase alfa</th></tr><tr><td>Motor</td><td>0.69 (0.48)</td><td>0.19 (0.56)</td></tr><tr><td>Language</td><td>0.58 (0.49)</td><td>0.13 (0.17)</td></tr><tr><td>Vision</td><td>0.55 (0.46)</td><td>0.23 (0.28)</td></tr><tr><td>Seizures</td><td>0.20 (0.62)</td><td>-0.17 (0.49)</td></tr></table></td><td></td><td></td></tr>
<tr><td>EAG report, Section 4.2.1, page 65–66, and Table 15 page 74</td><td>Change from<br>“CADHT” / “CADHTA”<br>to<br>“CADTH”</td><td>Correction of abbreviation</td><td>The EAG has corrected the abbreviation throughout the EAG report.</td></tr>
<tr><td>EAG report, Section 4.2.1, page 67</td><td>Change from<br>“Given the fundament differences in modelling approach….”<br>to<br>“Given the fundamental differences in modelling approach….”</td><td>Correction of spelling</td><td>The EAG has corrected this typo.</td></tr>
<tr><td>EAG report, Section 4.2.3, page 71</td><td>Change from</td><td>Clarity</td><td>The EAG has amended this statement as suggested by the company.</td></tr>
</table>

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "….and requirement for a feeding tube differs (see Sections 4.2.7.3 and 4.2.11.8)"<br>to<br>"….and requirement for a feeding tube ~~**differs**~~ (see Sections 4.2.7.3 and 4.2.11.8)" | | |
| EAG report, Section 4.2.4, page 72 | Change from<br>"The company preferred evidence source to inform the starting age…."<br>to<br>"The **company's** preferred evidence source to inform the starting age…." | Clarity | The EAG has corrected this typo. |
| EAG report, Section 4.2.4, page 72 | Change from<br>"Furthermore, the company key source of effectiveness ….."<br>to<br>""Furthermore, the **company's** key source of effectiveness ….." | Clarity | The EAG has corrected this typo. |
| EAG report, Section 4.2.4, page 72 | Change from<br>"….amongst general practitioners and GPs, which contribute…"<br>to | Correction of duplicated word and for clarity | The EAG has corrected this typo. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "….amongst general practitioners ~~**and GPs**~~, which **contributes**…" | | |
| EAG report, Section 4.2.4, page 73 | The company would like to flag to the EAG that the hyperlink "…mentioned in **section xxx**, study 190-203…" is missing | The cross-reference hyperlink is missing. | The EAG has removed the cross reference |
| EAG report, Section 4.2.7.1, page 77 | The company would like to flag to the EAG that the hyperlink "(see section 0)" is broken | The cross-reference hyperlink is broken | The EAG has updated the hyperlink. |
| EAG report, Section 4.2.7.1, page 78 | Change from<br>"….states that the MSN estimation models…."<br>to<br>"….states that the **MSM** estimation models…." | Correction of abbreviation | The EAG has corrected this typo. |
| EAG report, Section 4.2.7.1, page 80 | Change from<br>"….(all individuals with a baseline ML score of score)…."<br>to<br>"….(all individuals with a baseline ML score of **6**)…." | Correction of baseline ML score | The EAG has corrected this typo and has amended the text as suggested by the company. |
| EAG report, Section 4.2.7.1, page 82 | Change from<br>"…..cerliponase alfa and matched controls patients over time) ." | Removal of bracket | The EAG has corrected this typo. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | to<br>"…..cerliponase alfa and matched controls patients over time. | | |
| EAG report, Section 4.2.7.1, page 84 | Change from<br>"….as estimated by the MSN package…"<br>to<br>"….as estimated by the **MSM** package…" | Correction of abbreviation | The EAG has corrected this typo. |
| EAG report, Section 4.2.7.3, page 91 | The company would like to flag to the EAG that the hyperlink "(see section 0)" is broken | The cross-reference hyperlink is broken | The EAG has updated the hyperlink. |
| EAG report, Section 4.2.7.4, page 93 | Change from<br>"…higher proportion of these patients alive and/or in health states up to health state 6 over time compared to cerliponase alfa."<br>to<br>"…higher proportion of these patients alive and/or in health states up to health state 6 over time compared **with SoC**." | Correction of sentence | The EAG has corrected this typo and has amended the text as suggested by the company. |
| EAG report, Section 4.2.7.3, page 93 | Change from<br>"…that the original HST12 approach to modelling vision loss is more appropriate than the company" | Clarity | The EAG has corrected this typo and amended the text as follows:<br>"The EAG considers that the original HST12 approach to |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | to<br>"…that the original HST12 approach to modelling vision loss is more appropriate than the company **submission**" | | modelling vision loss is more appropriate than the CS […]" |
| EAG report, Section 4.2.7.4, page 93 | Change from<br>"…..as in the company's base case analysis some patients in the standard of care arm"<br>to<br>"…..as in the company's base case analysis some patients in the **SoC** arm | Correct abbreviation | The EAG has amended the text and used the abbreviation SoC. |
| EAG report, Section 4.2.7.5, page 93 | Change from<br>"…..only applied to individual in health state 9"<br>to<br>"…..only applied to **individuals** in health state 9 | Clarity | The EAG has corrected this typo. |
| EAG report, Section 4.2.8, page 95 and 96 | The company would like to flag to the EAG that the in-text cross-reference to Table 16 is incorrect, and should be replaced with a cross-reference to Figure 14 | Correction of cross-reference | This is not a typo. |
| EAG report, Section 4.2.8, page 96 | Change from<br>"The clinical adviser to the EAG suggested that while you might expect some treatment effect to remain between 6-9 months after cerliponase | Removal of 'but' | The EAG has corrected this typo and has amended the text as suggested by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | alfa discontinuation but you would not expect patients to remain for 3 years in these health state without treatment."<br>to<br>"The clinical adviser to the EAG suggested that while you might expect some treatment effect to remain between 6-9 months after cerliponase alfa discontinuation, ~~**but**~~ you would not expect patients to remain for 3 years in these health state without treatment." | | |
| EAG report, Section 4.2.9,<br>Page 97 | Change from<br>"….. to subject the child to regular infusions)."<br>to<br>"…..to subject the child to regular infusions." | Removal of bracket | The EAG has corrected this typo. |
| EAG report, Section 4.2.10.1, page 99 | Change from<br>"…..used to inform the company's base-case analysis[1]] is one of the studies"<br>to<br>"…..used to inform the company's base-case analysis[1] is one of the studies" | Removal of bracket | The EAG has corrected this typo. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 4.2.10, page 100 | Change from<br>"The resulting EQ-5D-5L scores were mapped to EQ-5D-3L values using the months) were mapped to EQ-5D-3L values using the Hernández Alava et al., 2020, algorithm"<br>to<br>"The resulting EQ-5D-5L scores were mapped to EQ-5D-3L values using the ~~**months) were mapped to EQ-5D-3L values using the**~~ Hernández Alava et al., 2020, algorithm" | Additional text has been incorrectly inserted | The EAG has corrected this text as suggested by the company. |
| EAG report, Section 4.2.19.3, page 104 | Add abbreviations to Table 22<br>Abbreviations: CS, company submission; EAG, external assessment group; MAA, managed access agreement; SoC, standard of care. | Correction of missing abbreviations | Thank you for indicating the lack of abbreviations. The EAG has added the abbreviations to Table 22. |
| EAG report, Section 4.2.10.3, page 104 | Change from<br>"…utilities derived from PedsQ™."<br>to<br>"…utilities derived from **PedsQL**™." | Correction of HRQoL measure | The EAG has corrected this typo. |
| EAG report, Section 4.2.11.12, page 116 | Change from<br>"The company's exclusion of the costs associated with psychiatric/behavioural support | Clarity | Thank you for indicating this. The EAG has corrected the sentence as suggested by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | for patients in health states 1-5 the NICE committee preferences in the original HST12”<br>to<br>“The company’s exclusion of the costs associated with psychiatric/behavioural support for patients in health states 1–5 **differs from** the NICE committee preferences in the original HST12” | | |
| EAG report, Section 6.1.1.3, page 128 | The company is not sure what the EAG meant by the following sentence and suggests this be rewritten for clarity;<br>“The EAG is particularly concerned about the uncertainty on whether the statistic model (fitted with the MSM R package) used by to estimate these parameters produces due to the unclear impact of using arbitrary initial values to inform the MSM models and the potential overfitting of these models to the observed data” | Clarity | The EAG has amended the text for clarity purposes. The current text is as follows:<br>“The EAG is particularly concerned about the uncertainty surrounding the transition probabilities estimated using the MSM R package. More specifically, the EAG is concerned about the unclear impact of using arbitrary initial values to inform the MSM models and the potential overfitting of these models to the observed data.” |
| EAG report, Section 6.1.1.5, page 129 | Change from | Correction of model health states associated with ML score | The EAG has corrected both typos. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "6.1.1.5 Scenario 6: Neuro-disability mortality for health states 6-9"<br>to<br>"6.1.1.5 Scenario 6: Neuro-disability mortality for health states **7–9**"<br>And<br>Change from<br>"…original HST12 might only apply to health states 6-9 (ML score 0)."<br>to<br>"…original HST12 might only apply to health states **7–9** (ML score 0)." | 0 and assumptions in EAG scenario. | |
| EAG report, Section 6.1.1.10 | Change from<br>"Clinical advice the EAG suggests that it is appropriate …."<br>to<br>"Clinical advice **to** the EAG suggests that it is appropriate" | Clarity | The EAG has amended the text as suggested by the company. |
| EAG report, Section 6.2, page 131 | Change from<br>"ICERs cerliponase alfa vs. SoC"<br>to | Clarity | The EAG has amended the text as suggested by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | "ICERs **for** cerliponase alfa vs. SoC | | |
| EAG report, Section 6.2.1.10, page 139 | Change from<br>"Table 40 presents the cost-effectiveness results of scenario 11, where the EAG includes the costs of ECG monitoring in line with the NICE committee's preferences for the original HST12."<br>to<br>"Table 40 presents the cost-effectiveness results of scenario 11, where the EAG includes the costs of **psychiatric/behavioural support** in line with the NICE committee's preferences for the original HST12." | Table 40 presents the scenario relating to psychiatric/behavioural support | The EAG has corrected this typo. |
| EAG report, Section 6.3, page 140 | Please amend all instances of "ML score of 0" to state "ML score of **6**" | Correction | The EAG has corrected this typo. |
| EAG report, Section 6.4, page 145 | Change<br>"….. the baseline distribution of patients across health states (additional analysis ; the source used to inform transitions (additional analysis 3) and the treatment discontinuation rule (additional analysis )"<br>to<br>"….. the baseline distribution of patients across health states **(additional analysis 1)**; the | Correction | Thank you for indicating these typos. The EAG has corrected them. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | source used to inform transitions (additional analysis 3) and the treatment discontinuation rule **(additional analysis 4)"** | | |

**Issue 4 Errors in confidential mark-up**

| Location of incorrect marking | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 5.1.1, page 117 | Change from<br>"The company's base-case deterministic analysis suggests that compared to SoC, the cerliponase alfa is costlier by [redacted] and more effective resulting in 17.35 incremental QALYs, yielding an ICER of [redacted] per additional QALYs."<br>to<br>"The company's base-case deterministic analysis suggests that compared to SoC, the cerliponase alfa is costlier by [redacted] and more effective resulting in 17.35 incremental QALYs, yielding an ICER of [redacted] per additional QALYs." | Unredacted list price ICERs can be used to back-calculate the PAS price for cerliponase alfa. | The EAG has updated this, but notes that this ICER considers the acquisition cost of cerliponase alfa at list price and not with the PAS price. |

**Issue 5 Errors in reporting of economic model results**

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>EAG report, Section 4.2.8, page 95</td><td>Change Figure 14 value 0.75% (from state: 6, to state: 7) to not be highlighted.</td><td>Correction, highlighted values in Figure 14 represent those adjusted for discontinuation. This transition has not been adjusted for discontinuation.</td><td>The EAG has amended this.</td></tr>
<tr><td>EAG report, Section 5.1.2, page 118</td><td>The EAG note that “Probabilistic results are presented in“ but do not further specify, the company believe a table may be missing and the following should be presented.
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>SoC</td><td>[redacted]</td><td>-0.14</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Cerliponase alfa</td><td>[redacted]</td><td>17.50</td><td>[redacted]</td><td>17.64</td><td>[redacted]</td></tr>
</table>
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.</td><td>Correctly present probabilistic results</td><td>The EAG has amended this.</td></tr>
<tr><td>EAG report, Section 5.1.2, page 119, Table 26, row Scenario: MAA (all</td><td>Change from<br>“[redacted]”<br>to<br>“[redacted]”</td><td>The result is incorrectly reported</td><td>The EAG has amended this.</td></tr>
</table>

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| patients), treatment-independent utility values", column "% change from base-case ICER | | | |

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>EAG report, Section 5.1.2, page 119, Table 26, row “Scenario: Include testing costs”</td><td>Change row results from<br><table><tr><th></th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th><th>% change from base-case ICER</th></tr><tr><td>Scenario: Include testing costs</td><td>[redacted]</td><td>17.35</td><td>[redacted]</td><td>[redacted]</td></tr></table>To<br><table><tr><th></th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th><th>% change from base-case ICER</th></tr><tr><td>Scenario: Include testing costs</td><td>[redacted]</td><td>17.35</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>The results are incorrectly reported</td><td>The EAG has amended this.</td></tr>
<tr><td>EAG report, Section 6.2, page 131</td><td>Change from<br>“these ICERs are higher than the company’s base case ICER ([redacted] per additional QALY)”<br>to<br>“these ICERs are higher than the company’s base case ICER ([redacted] per additional QALY)”</td><td>The ICER is incorrectly reported</td><td>The EAG has amended this.</td></tr>
</table>

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| EAG report, Section 6.3, page 141 | Change from<br>"In the EAG's deterministic base-case both the incremental costs and incremental QALYs for cerliponase alfa vs. SoC decreased compared to the compared to the company's base-case ([redacted] vs. [redacted]; 9.91 vs. 17.07 QALYs)"<br>to<br>"In the EAG's deterministic base-case both the incremental costs and incremental QALYs for cerliponase alfa vs. SoC decreased compared to the compared to the company's base-case ([redacted] vs. [redacted] ; 9.91 vs. **17.35** QALYs)" | The incremental QALYs for the company base case are incorrectly reported | The EAG has amended this. |
| EAG report, Section 6.3, page 142, Table 41 | Please correct the results for Analysis 7. | These results are identical to the row below; the ICER should be [redacted] | The EAG has amended this. |
| EAG report, Section 6.3 | Please correct the PSA results for the EAG base case. | The result of [redacted] contains an excess digit | The EAG has amended this. |

### Issue 6 Economic model errors

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Engine_CA & Engine_SoC column BG | The additional formulae added by the EAG for the number of people who are blind incorporates the proportion of patients who are dead. This will overestimate the impact of vision loss on costs and QALYs.<br>e.g. Engine_SoC, cell BG18<br>• Current: =SUM(BC18:BF18)<br>• Proposed amendment: =SUM(BC18:**BE18**)<br>e.g Engine_CA, cell BG18<br>• Current: =SUM(BC18:BE18)+(Engine_SoC!BG18-SUM(Engine_CA!BC18:BF18))<br>• Proposed amendment: =SUM(BC18:BE18)+(Engine_SoC!BG18-SUM(Engine_CA!BC18:**BE18**))<br>Or<br>=Engine_SoC!BG18, once the proposed amendments to Engine_SoC column BG, as specified above, are made. | Correction of formulae.<br>Please note that as cerliponase alfa is expected to delay disease progression compared with SoC, patients in the SoC arm are expected to die more quickly. Therefore, the proportion with vision loss in the cerliponase alfa arm will account for deaths in the SoC arm. | This is not a model error. It was modelled in line with original HST12 appraisal. |
| Engine_CA column EX | The EAG amended formulae to incorporate the cost of ECG at treatment infusion does not adjust for the proportion of patients who are on treatment. This will overestimate the cost of ECG.<br>e.g. Engine_CA, cell EX18 | Correction of formulae | This change has been implemented and the affected results have been updated to reflect this change. |

| | | | |
|---|---|---|---|
| | • Current: =IF($A$1=2,0,BZ18*$EX$10)+IF('Cell links'!$O$12=1,0,Engine_CA!EW18*'Cost data'!$C$330+(1-Engine_CA!EW18)*'Cost data'!$C$330/26)<br>• Proposed amendment: =IF($A$1=2,0,BZ18*$EX$10)+IF('Cell links'!$O$12=1,0,Engine_CA!EW18*'Cost data'!$C$330+(1-Engine_CA!EW18)*'Cost data'!$C$330/26)***BZ19** | | |
| Engine_CA & Engine_SoC, Column CV | The EAG formula for the vision loss utility multiplier applies a multiplier of 0.87 to the proportion of the overall population with vision loss, rather than the proportion of alive patients with vision loss. This means that the multiplier initially decreases before decreasing again.<br>e.g. Engine_CA and Engine_SoC cell CV18<br>• Current: =(1-CF18)*1+CF18*CH18<br>• Proposed amendment: = **(1- (CF18/(1-BF18)))*1 + (CF18/(1-BF18))*CH18** | Correction of formulae | This is not a model error. It was modelled in line with original HST12 appraisal. |

NICE National Institute for Health and Care Excellence

# Highly Specialised Technology

# Guidance review following a period of managed access

# Clinical expert statement

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

| **About you** | |
|---|---|
| 1. Your name | **Paul Gissen** |

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| 2. Name of organisation | **Great Ormond Street Hospital** |
| 3. Job title or position | **Professor and Honorary Consultant in Paediatric Metabolic Medicine** |
| 4. Are you (please tick all that apply): | ☐ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with this condition?<br>☐ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |

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| 6. Do you have a conflict of interest that you wish to declare[1]? | Direct – please explain<br><br>I have been chief investigator for BioMArin sponsored trials of cerliponase alfa and my organisation received research grants, I received honoraria for attending advisory board meetings and speakers fees from BioMarin. |
| 7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☐ yes |
| **The aim of treatment for this condition** | |
| 8. What is the main aim of treatment? | For cancer drugs please delete as appropriate: curative / stop progression / palliative<br><br>Other, please describe<br>Cerliponase alfa is an enzyme replacement therapy for a genetic disorder caused by deficiency of TPP1 lysosomal enzyme. The aim of treatment is to provide a replacement TPP1 enzyme and correct its deficiency in brain cells. This replacement will restore the function of the brain cells and prevent/slow down the deterioration of body functions dependent on normal brain activity. |

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

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| 9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.) | I consider substantial slowing down of disease progression as a significant response. |
| 10. What are the benefits that you expect the technology to provide compared with routinely commissioned care? | Health benefits. Please delete as appropriate:<br><br>Increased survival Y<br><br>Increased time to progression Y<br><br>Improved QOL Y<br><br>Does the new technology provide other substantial health related benefits not included in the QALY calculation? Y,<br>please explain: The QALY calculations do not take into account the difference in communication and perception of surroundings that are preserved in patients on treatment.<br><br>Non-health benefits. Please delete as appropriate:<br><br>Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y,<br>please explain: Improvement in communication and general wellbeing of the patients also improves the quality of life of the carers. Moreover, the slowing down of disease progression means that the parents and |

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| | the family have longer time to enjoy life with their children whilst they are still able to move and communicate.<br><br>Improved accessibility to patients Y, please explain: The patients on treatment have longer time still able to mobilise, appreciate life around them, enjoy communication.<br><br>Implications for delivery of the NHS service Y, please explain:Patients remain in better state for longer and therefore use less of the palliation. However, the treatment itself requires a lot of the NHS effort because these are two weekly intracerebroventricular infusions. |
| 11. Are there any recognised side effects of the technology? | If yes, please explain how they may affect the patient's quality of life.<br><br>The main side effect of the technology is the need for hospital attendance for the four hour infusions.<br>Patients may develop hypersensitivity reactions but these are relatively easily managed. |
| 12.Are there any important outcome data that were not collected during the managed access period? | no |

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| 13. In your view, what is the unmet need for patients and healthcare professionals in this condition? | Without the treatment with cerliponase alfa patients with CLN2 suffer distressing progression to very severe state. Cerliponase alfa treatment means that the patients remain in much better state for many years.<br>However, despite the intracerebroventricular infusions of cerliponase alfa most of the patients suffer from vision loss which account for the loss of quality of life with time.<br>Visual loss is a major unmet need. This can be prevented by intravutreal cerliponase alfa infusions or, potentially, in the future, by gene therapy in the eye.<br>Another unmet need is the early diagnosis. It has now become apparent that patients treated pre-symptomatically remain in much better state for a lot longer than patients treated after the symptoms started. Hence, newborn screening is the only way to achieve early detection. |
| 14. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? | Yes cerliponase alfa transformed the way we perceived the disease. CLN2 disease is now considered a treatable condition. |
| 15. Are there any groups of patients who might benefit more or less from the technology than others? | The earlier in the disease progression the treatment is started the better the outcomes seems to be in the long-term follow up. Early treatment prevents progression of dystonia and spasticity, which means patients remain in better physical condition and also can communicate better. |

| What is the expected place of the technology? | |
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| 16. How is the condition currently treated in the NHS?<br><br>• Are any clinical guidelines used in the treatment of the condition, and if so, which? | No, please provide a link:<br>The only disease specific treatment for CLN2 is cerliponase alfa provided on Managed Access Agreement, which has been agreed by NICE. |
| 17. Are there other clinical pathways used in England other than those recommended in the guideline? | No, please explain important differences and why they occur: |
| 18. Would the new technology require a change in the clinical pathway? | Once approved the clinical pathway can be simplified and certain parts of the managed access agreement can be removed. |
| 19. Will the technology introduce new costs to the NHS or patients other than for the technology itself? | The patients treated with cerliponase alfa will live longer and will remain in much better state compared with the patients who are not treated. Nevertheless, unless the treatment can start pre-symptomatically the patients will require clinical follow up and management of the symptoms such as movement disorders and sight loss (unless specific treatments to preserve sight are instituted). |

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| 20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned?<br><br>If not, how would starting and stopping criteria be adapted? | There are starting and stopping criteria used for managed access agreement. In my opinion these criteria can also be used when cerliponase alfa is commissioned. Although it can be slightly modified. For example the quality of life scales can be used differently to apply to stopping criteria. |
| **What was your experience of the technology during the managed access agreement [MAA]?** | |
| 21. What has been your experience of administering the technology during the period of the MAA? | Positive: I can see how much this drug changed the lives of patients and their families to the better.<br><br>Negative: The fact that the families had to travel to the hospital every two weeks is a big burden to the families. I believe this is much improved now that several local centres are opened for drug administration. |
| 22. Did any people decline treatment? What were their reasons why? | Yes. We had one family with one patient who decided not to start with the infusions as they believed that for them two weekly infusions provided in the hospital was too much of a burden. There was another family with two affected children who decided to stop after 6 months. The travel for this family was even longer and they felt that on balance this was not for them. |

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| 23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA? | Certain assessments were difficult to organise (especially during the COVID pandemic) for example brain MRI scans, EEGs, OCT, psychology assessments. I think that when the drug is commissioned the yearly MRI scans, EEGs and OCTs can be dropped and only performed when clinically indicated. Psychology assessments are very useful to look at the cognitive development, however, the NHS shortage of psychologists is a big problem. |
| 24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How? | Yes as mentioned above. I think we can get rid of brain MRIs (we know now what to expect because of the research and the MAA data), OCT (similarly we know what to expect), EEGs (no clinical benefit unless indicated). I think it is important to continue with 1-2 yearly cardiology assessments. |
| 25. Are there other points of learning arising from the period of the managed access agreement that you would like considered? | When consider the loss of points on quality of life assessments (as a stopping criteria) it is best to compared to the original score rather than the score from the year before. |
| **Sources of evidence** | |
| 26. Are you aware of any new relevant evidence that might | Yes for the technology, please give link: No |

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| not be found by a systematic review of the trial evidence? | Yes for the comparator, please give link: No |
| **Topic-specific questions** | |
| **27. Key issue 6:**<br>• At what age are people currently diagnosed with CLN2?<br>• Which baseline distribution across health states best reflects that of people initiating treatment in clinical practice? (Distribution 1 - HS1: 50% HS2: 50%, Distribution 2 - HS1: 87.5% HS2: 12.5% or other)<br><br>*HS1 and HS2 = motor and language (ML) scores of 6 and 5 on the adapted version of the four-domain Hamburg scale measure, the CLN2 clinical rating scale, which includes the motor and language domains* | I have just reviewed a group of classical CLN2 patients that we treated at GOSH with cerliponase alfa.<br><br>Out of the 19 patients only 5 were diagnosed earlier than age 4 and 2 of those were diagnosed due to siblings. The rest of the patients were diagnosed between the ages of 4 years and 4 years and 11 months.<br><br>There were several patients diagnosed after the age of 5 but they were too progressed and not eligible according to the starting criteria.<br><br>Among the group of the 19 classical CLN2 patients (mentioned above) 2 patients had ML score of 6 (HS1) and 2 patients had score of 5 (HS2). 11 children had ML score of 4, 2 children score of 3 (2+1). 2 of the children were non-verbal and therefore language domain was not scored but they scored 2 and 3 on motor domain. |

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| *of the scale and excludes the vision and seizure domains.*<br><br>• Are age and ML score distribution at diagnosis expected to change in the near future? If so, why? | I suspect that the age at diagnosis will come down slightly with better education however the only way to significantly change the tendency to early diagnosis is to bring newborn screening. |
| **28. Key issue 7:**<br>• What proportion of people that start treatment with a ML score of 6 would you expect to be "initial stabilisers"? (100%, 80% or other)<br>*Initial stabilisers = All remain in HS1 for the first 6 years in the model. Beyond 6 years, transitions to worse health states occur at half the rate of the transition probabilities applied to those who enter the model with a worse ML score.* | I suspect that at least 80% of patients with the score of 6 will be early stabilisers. |
| **29. Key issue 10**<br>• When does vision loss start for most people with CLN2, and by what age on average would people completely lose their vision?<br><br>• Do you expect cerliponase alfa to improve or stabilise vision loss in the long-term? | There is some variability in the speed of vision loss. Some patients have very reduced vision by the age of 5.5 but some have reasonable vision at the age of 9. I suspect the majority will have functional sight loss by the age of 6.<br><br>Cerliponase alfa will only be able to improve sight loss in all children if delivered via intravitreal injections. |

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| **30. Key issue 11:**<br>• In clinical practice, when would you expect cerliponase alfa to be discontinued?<br><br>• Would you expect a treatment effect to remain after discontinuation of cerliponase alfa? | This would have to be made on balance between pros and cons and depends on the perception of quality of life of the families. It is likely that the treatment brings some benefits even to patients with significantly progressed disease: e.g. some stabilisation in seizures, myoclonus, prevention of severe spasticity, preservation of communication. However, this perception is not the same for all families. |
| **Equality** | |
| 31. Are there any potential equality issues that should be taken into account when considering this treatment? | There is an issue of equality of access where some patients who live in remote areas do not have easy access to the treatment centres. |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

# Highly Specialised Technology

# Guidance review following a period of managed access

# Patient expert statement

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1.Your name | **Liz Brownnutt** |

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| 2. Are you (please tick all that apply): | ☐ a patient with the condition?<br>☐ a carer of a patient with the condition?<br>☑ other (please specify): I am a family member who has been affected by CLN2 Batten disease. My niece and nephew were both diagnosed 10.5 years ago, and both sadly passed away aged 6 and 9 respectively. Neither child ever had cerliponase alfa |
| 3. Did your nominating organisation submit a submission? | ☑ yes, they did *<br>☐ no, they didn't<br>☐ I don't know |
| 4. How did you gather the information included in your statement? (please tick all that apply) | ☑ I have personal experience of the condition *<br>☐ I have personal experience of the technology being appraised<br>☑ I have other relevant personal experience. Please specify what other experience:<br>I have worked at the BDFA for 3.5 years and through this I have had contact with many other families affected by CLN2 Batten disease and whose children are receiving cerliponase alfa<br>☑ I am drawing on others' experiences. Please specify how this information was gathered:<br>- Personal lived experience<br>- Families' experience through regular contact as part of my work at the BDFA<br>- BDFA submission and family and education surveys<br>- Company SIP |

| Living with the condition | |
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| 5. What is it like to live with the condition? Consider<br><br>• the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships and social life).<br><br>• if you are the parent of an affected child, include their ability to go to school, develop emotionally, form friends and participate in school and social life. | I agree with the points made in the BDFA submission, which contains details of the symptoms of CLN2 disease. My following comments are a personal account of my experience of how the disease affects the family.<br><br>A diagnosis of Batten disease has a devastating impact on the whole family. As a family member it is shocking to learn that a child you have known for several years, who was born healthy and who is enjoying normal family relationships with you and your children, will gradually lose all their skills, become completely dependent on their parents for all their needs and will ultimately not be able to recognise you. At the point of diagnosis this seems imperceivable to every loved one of a child diagnosed with Batten disease.<br><br>My experience of my own family and that which I have seen of families supported by the BDFA is that their lives are turned upside down as they struggle to cope with their child's rapidly changing complex needs, managing a range of appointments and interventions from medical and other professionals that arrive in their life. Families face many challenges, particularly with a 'postcode lottery' of care and support, depending on where they live in the UK. Many face extreme isolation, often with no family living nearby and a limited support network. They are effectively grieving from the day of diagnosis, and many feel isolated, coping with 'anticipatory grief'. The shift from 'parent' to 'parent carer' is challenging and parents increasingly take on complex nursing tasks.<br><br>Many families experience significant financial challenges as their caring responsibilities become greater and one or both parents have to give up work to care for their child. Some families, including my own, have two children affected by CLN2 disease meaning that even if one parent was still able to work, there is a need for a great degree of flexibility to their working pattern. Many employers are sympathetic, as was the case for my family, but in reality not all might be.<br><br>Families often have to fight in order to get the benefits they are entitled to. An example of this is that my niece was not awarded the higher rate of mobility allowance, which would have enabled her parents to get a car, because she wasn't officially sick enough. |

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| What is the effect on any siblings?<br><br>• what carers experience when caring for someone with the condition | The DWP had already put her younger brother on the higher rate, even though he was a year behind his sister with the disease and still walking (his sister was in a wheelchair). My family had to appeal the decision twice and were told that my niece just didn't qualify, although no-one could explain why her brother did. The decision was only reversed when their local MP contacted the Head of the DWP. When families are already dealing with so much, it is hard to understand why they have to go to such lengths just to get what they are entitled to.<br><br>Funding for adaptations to the home is an ongoing issue for families and the process of applying for a Disabled Facilities Grant can be lengthy and frustrating. The DFG is mainly not sufficient to carry out all the adaptations needed and families often find themselves having to fundraise or are reliant on relatives to support them financially. For many time that should be spent with their children is spent chasing funds for their care. This was the case for my family, and I personally supported them through writing to some trusts and Foundations for support. |
| 6. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition?<br>What was the impact of this on you and your family? | My niece was 5 when she was diagnosed and had experienced a 19-month diagnostic journey, during which time the disease was fast-progressing. Her brother experienced his first seizure during this time. The diagnostic journey was extremely stressful and flawed with inconsistencies and delays.<br><br>My niece had her first seizure in May 2012 at age 3 years and 5 months and her parents had already been told by the Special Educational Needs Coordinator (SENCO) at her pre-school that she was not progressing as expected, so it was presumed the epilepsy was part of a larger problem quite quickly. But the family's diagnostic journey does not suggest that there was any urgency to finding out what the underlying issue was.<br><br>The speed at which both children were impacted by the disease was shocking to witness. My niece walked to school on her first day in September 2013, but she was in a wheelchair six weeks later.<br><br>By the time my nephew first had a seizure, his sister had already regressed mentally, and they were no closer to a diagnosis. At this stage their parents were told that they might be able to halt my nephew's regression, but not reverse it. |

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| | My brother-in-law stated that as his son hadn't yet regressed then the diagnosis had to be prioritised so that the deterioration could be halted before it got too bad. He suggested that the Paediatric Neurologist had my nephew in for a day to do every test possible, but he was told that isn't how things are done. What followed was a process of blood tests every other month and the family were told that the blood tests had a turnaround time of 6-8 weeks. They were not carried out in their home city's hospital but sent down to Great Ormond Street Hospital on specific days. On one occasion the test wasn't completed because the hospital had not been able to read the Paediatric Neurologist's instructions. My brother-in-law was not told this until eight weeks later when he called for the results, so that was a wasted 16-week period, waiting for the results for the retaken test, with no answers or progression.<br><br>Once my nephew had epilepsy, the procedures did increase. Both children would have physical assessments, blood tests, procedures (MRI/Lumbar/ECG), but never at the same place and never at the same time. The family went through weeks where they had six appointments for the children, all at different places.<br><br>Fifteen months after my niece's first seizure, my brother-in-law urged his GP (who was extremely helpful) for some support regarding test results. He told him that, in the separate tests the children were having, both had references to having a small cerebellum, and my brother-in-law wondered if this could be connected. As the children were not seen together until after the diagnosis, it seemed that the connection with these results had not been made. My brother-in-law's questions regarding it, passed on by his GP, were not taken up by the hospital, and they continued down other paths, looking for answers, for another 4 months.<br><br>On December 17th, 2013, the family had an appointment with a Paediatrician. They complained to her about not having been given results to previous tests so she looked at my niece's file onscreen, and there was a letter from the Paediatric Neurologist, which she told them referred to a reduced cerebellum and a neurodegenerative disorder, but she said that she couldn't say anymore as it wasn't her place to do so.<br><br>The family then went back to the Paediatric Neurologist but could only get through to the hospital secretary. Again, the family contacted their GP to try to find out what was happening, but they didn't get the appointment with the Paediatric Neurologist, where they were finally given the possible CLN2 Batten |

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| | disease diagnosis for a further four days. The diagnosis was subsequently confirmed through specific blood testing.<br><br>Our family feels very strongly that the time taken for a diagnosis for my niece and nephew could have been shortened considerably and it is sad and unacceptable that they had to fight every step of the way.<br><br>My family saw the diagnosis as simply being the point at which they gained understanding. They felt that there seemed to be no urgency to get there from anyone except them.<br><br>No family should experience what they went through, and it was hard as an extended family member to witness their journey. |
| **Current treatment of the condition in the NHS (outside of the managed access agreement [MAA])** | |
| 7. What do you think of current treatments (if they exist) and care available on the NHS (outside of the managed access agreement)? What are the things they do not do well enough? | I agree with the points made in the BDFA submission and would like to reiterate that families face a 'postcode lottery' of care depending on where they live with no clear care pathway that brings together health, social care and education from the point of diagnosis. Families have to fight to access some services and all the time the disease is progressing rapidly. In the case of my family, it seemed that there was no urgency regarding some aspects of health care, that could have particularly given my niece a better quality of life.<br><br>For example, it took 6 months for a referral for a feeding tube for my niece, by which time the disease had progressed rapidly and she could no longer eat. Her parents have expressed that if she had been prioritised then she would have had the nutrition that enabled her to build much-needed physical resilience. The diagnosis they were given for my niece was that she had perhaps 10 years, but she only survived a further 18 months from that point.<br><br>In relation to education and social care, the delay my family experienced in getting my niece transferred from mainstream school to a special school was hampered by lack of communication within social services regarding the statement. |

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| | When it was finally complete, the wrong school had been identified and so the process had to restart. Then it took two months for transport to be organised and this was only resolved when the local MP got involved. The whole process of getting a statement and moving to the named special school took two years and was only completed two weeks before my niece died. |
| 8. Is there an unmet need for patients with this condition? | I agree with the points made in the BDFA submission and would like to emphasise that having lost two precious family members to CLN2 disease and having witnessed the rapid decline that they experienced, it is imperative that the time to diagnosis is shortened to enable patients to access treatment at the earliest opportunity and patient care pathways need to be vastly improved to give patients and their families a better quality of life. |
| **What was the experience of the technology during the managed access agreement [MAA]?** | |
| 9. What has been the experience of having access to the technology during the period of managed access? | I agree with the BDFA submission on this point and have no further comments. |
| 10. How has the technology fitted in with other treatment and care for the condition? | I agree with the BDFA submission on this point and have no further comments. |
| 11. Describe how receiving the technology has impacted everyday life. Has it had an | I agree with the BDFA submission on this point and have no further comments. |

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| impact on what carers experience? How? | |
| 12. How easy or difficult is it to take/have the treatment? How does this impact you and your family (for example, travel or how the treatment is received? | I agree with the BDFA submission on this point and have no further comments. |
| 13. What place do you think the technology has in future treatment and care? | I agree with the BDFA submission and would also add that my family's experience was 11 years ago and sadly there are still delays to diagnosis and a lack of specific care pathways. |
| **Advantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])** | |
| 14. What do you think are the advantages of the treatment? Consider the impact on everyday life and anything you described in the 'living with the condition' section. | I agree with the BDFA submission on this point and have no further comments. |

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| **Disadvantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])** | |
| 15. What do you think are the disadvantages of the technology? Consider the impact on everyday life and anything you described in the 'living with the condition' section. | I agree with the BDFA submission on this point and have no further comments. |
| 16. Are there any side effects? What are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? | I have no comment to make |
| **What was measured during the managed access agreement [MAA]?** | |
| 17. Thinking about the things that got measured during the | I agree with the BDFA submission on this point and have no further comments. |

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| period of the managed access agreement (MAA), do you think that all the things that were important were measured?<br><br>Please list what they were and why they were important (or unimportant) | |
| 18. Were there things that were not measured but are important to you?<br><br>If there were, please list what they were and why they were important. | I agree with the BDFA submission on this point and have no further comments. |
| **Patient population (including experience during the managed access agreement [MAA])** | |
| 19. Are there any groups of patients who might benefit more or less from the treatment than others? If so, | I agree with the BDFA submission on this point and have no further comments. |

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| please describe them and explain why. | |
| **Equality** | |
| 20. Are there any potential equality issues that should be taken into account when considering this condition and the treatment? | I agree with the BDFA submission on this point and have no further comments. |
| **Other issues** | |
| 21. Are there any other issues that you would like the committee to consider? | Batten disease is utterly devastating and has a lifelong impact on the family. All family members are affected; siblings, grandparents, aunts, uncles and cousins. My children experienced the loss of their cousins at such young ages, something you would never want for them. Writing this statement and reliving some of the difficult experiences that my family went through has been challenging, but I do not wish for the loss of my niece and nephew to be in vain. I sincerely hope that all patients with CLN2 disease and those diagnosed in the future will continue to benefit from cerliponase alfa and that agencies will implement ways to shorten the time to diagnosis and improve care pathways, so that patients will receive the benefit of the treatment at the earliest opportunity and have a good quality of life. |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1.Your name | **Mrs Gail Rich** |

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| 2. Are you (please tick all that apply): | ☐ a patient with the condition?<br>**Y** a carer of a patient with the condition?<br>☐ other (please specify): |
| 3. Did your nominating organisation submit a submission? | **Y** yes, they did<br>☐ no, they didn't<br>☐ I don't know |
| 4. How did you gather the information included in your statement? (please tick all that apply) | **Y** I have personal experience of the condition<br>**Y** I have personal experience of the technology being appraised<br>N I have other relevant personal experience. Please specify what other experience:<br>**Y** I am drawing on others' experiences. Please specify how this information was gathered: |
| **Living with the condition** | |
| 5. What is it like to live with the condition? Consider<br>• the experience of living with the condition and the impact on daily life (physical and emotional | Life with Batten Disease is utterly devastating and all consuming. -<br>The word 'heartbreaking' is used often, but what we experienced when we were given a diagnosis was a physical pain, like our hearts were literally breaking, hearing those words reverberated in our heads and we felt we could not breathe with the weight of an unbearable grief because we had to accept we could not change the outcome.<br><br>It takes away all of the hopes and dreams you had when your precious child was placed in your arms for the first time and you held them tight, promising to love and protect them forever.<br>After watching them attain skills and abilities, proudly sharing with family and friends, you then watch them begin to struggle doing these joyous thing for a reason unbeknown to you. |

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| health, ability to work, adaptations to your home, financial impact, relationships and social life).<br><br>• if you are the parent of an affected child, include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?<br><br>• what carers experience when caring for someone with the condition | Then to find out your child (in our case, children) have a life limiting illness is utterly horrifying and the profound grief and despair this places on parents is very difficult to articulate.<br><br>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.<br><br>You will slowly witness the 'last' of things. The last time they say your name, the last time they drink from a cup, the last time they can run, walk, climb….and you have the heartbreaking knowledge that this is never going to get better. (without treatment)<br><br>It cannot be underestimated how this destroys and crushes parent's lives. Everything we were, everything we did, everything we found security with, had gone.<br><br>Relationships are strained as you are unable to do what you once did, you can't continue in the social pursuits anymore because your world has been flipped on it's head. You stop going out, you retreat, you recover, you get knocked down again, you climb back up and so the cycle continues. Resilience is exhausting but somehow you find the strength to keep going, because your children need you.<br><br>You find you are having to rethink, rebuild and traverse a forever changing landscape of your once certain and predictable life path.<br><br>**Physical impact**<br><br>For parents who are caring for their child, the physical impact include; sore backs, aches and pains from lifting and carrying. There is disparity across the country where it seems to be a postcode lottery to receive the appropriate equipment and adaptions. We have been very fortunate in our experiences of getting the right adaptive equipment for our oldest daughter when she needed it with minimum wait times, apart from getting hoists in which was a huge problem and led to my husband having very severe back pain.<br><br>I know some families have had unacceptable waiting periods for essential pieces of equipment to support their child which is very sad.<br><br>**Impact on mental health** |

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| | The impact on mental health is a huge issue for parents of children with Batten Disease.<br>It is difficult to accurately describe the burden that such a horrendous disease has and the complexity and numerous afflictions/symptoms relating to the disease as it progresses which all require separate interventions, places a continuous strain on our mental health.<br>The weight of fear, anxiety, guilt, grief, pain and anguish is overwhelming.<br>The feelings of despair run incredibly deep. Our world was rocked to the core and we are then forced to try and find the strength to pick ourselves up and immediately become rare disease experts, equipping ourselves with knowledge of this unknown beast of a disease.<br>Then we have to accept that we are now part of the rare disease world which has many inequalities and disparities so we then find ourselves facing multiple barriers, complicated procedures for accessing services, fighting for our child to get access to treatment, equipment, personal care items to name a few. It is exhausting.<br>Add this to trying to raise the affected child's siblings who have their own needs and you will get a slight glimpse into the mindset of batten parents and how our mental state is impacted.<br><br>Parents are living in mental turmoil and I would describe my feelings over the years as living in a constant state of alertness with little to no let up. Most of the time it does not dominate my every day activities but it is always there.<br><br>Life with Batten Disease is so unpredictable due to the uncertain nature of the condition therefore maintaining a 'normal' social life is pretty difficult so that is another loss to parents that we have to accept.<br><br>Anticipatory grief is another toll on parents because the nature of this horrid condition, you feel like you are slowly losing your child as they progress. It is a sorrowful and heart-wrenching emotion to have to shoulder every day. You are grieving the child they used to be and also you are grieving the child you had dreamt of them becoming.<br><br>**Social**<br>Before our oldest daughter was diagnosed and began treatment, she would get incredibly agitated and regularly cry and scream for no apparent reason. We stopped going out because it was too stressful and upsetting to be unable to predict these outbursts and then to be unable to settle and sooth her. |

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| | Linking this to the impact of battens on siblings, it was really hard for our son during this phase of our daughter's journey because he was geared up and excited to go places but inevitably, we would have to cut our visit short. He would be upset that we couldn't do what everyone else was able to do.<br><br>The way Battens dictates how you live your life is all consuming.<br><br>Gone were the days of being carefree, grabbing our coats and going on spur of the moment adventures. We instead had to consider and organise our trips with a military like precision considering every possible scenario we could encounter. Snacks, Ipads, chargers, medicines, accessibility issues, personal care facilities, sensory toys, headphones, food, drinks, fans, sunshades, rucksacks (because you need your hands free at all times – a normal bag is out of the question) everything is considered and practicality and functionality are top priorities.<br><br>Following treatment, our daughter was like a different girl. She was instantly settled, the outbursts stopped and so very slowly we began venturing out again. It took time because our confidence and energy levels had been depleted but we did it. We got a little bit of our life back because of Cerliponase Alfa.<br><br>**Schooling**<br>Our daughter started at a specialist school shortly after she was diagnosed in 2016 and it was the most incredible place for her. She enjoyed many years of fun, exciting adventures and activities, love, socialising, trying new things, making friends the list of positives is endless! As our daughter's condition changed the activities changed with her so she (and ourselves) never felt like she was missing out. She was attending rebound, hydrotherapy and massage sessions regularly throughout the week and used eye gaze technology every week too. She enjoyed immersive theatre groups and had the best time with the best people.<br>She enjoyed those things and her life was richer as a result and this was all because of Cerliponase Alfa.<br><br>**Impact on siblings** |

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| | Our son has been profoundly affected by Batten Disease and the impact this has had on his sisters and our family life.<br><br>He has watched his best friend and partner in crime, his little sister lose her abilities during his childhood which meant he was unable to continue to play the same games as they always did as she needed increasingly more help.<br>During his childhood he expressed the most heartbreaking feelings of guilt at the fact that he was healthy and often used to ask “Have I just been lucky Mammy?”<br><br>He has said such things as “I wish I could give her my legs so she could still walk” and expressed feeling of sorrow for his sister and what she had lost and could no longer do.<br><br>He has witnessed his sisters having seizures and stood in the background as we frantically called for ambulances and watched as the paramedics came in to our home and help his sisters. He has witnessed incredibly traumatic events which would induce a state of panic and trauma on adults never mind a child. We had three children who all needed us just in very different ways and that is difficult to balance in your mind. The practical necessity of hospital and spending more time with the girls but the emotional impact for the sibling who may feel like they always have to come second, which they may interpret as meaning they are less important is something we have been very conscious of. We have had to divide our time and any respite we had we would make sure we dedicated that to quality one on one time with our son.<br><br>From a young age he was impacted by separation of our family unit as we left him at home while we took the girls to hospital for their treatment.<br><br>When our son was around 7yrs old, we sought help with some significant changes in his behaviour – he was displaying a lot of anger and aggression and saying very unkind and upsetting things about his sister but he was still so young and so innocent, we encouraged him to share his feelings but it was heartbreaking to listen to. We knew he didn’t mean the things he was saying and I certainly knew he loved and adored his sister, he was just struggling to place the source of his feelings.<br>He began a period of play therapy where a play therapist would visit our home and devote an hour a week to spending time with him and playing games he enjoyed. |

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| | When the sessions were at an end the therapist concluded that our son was angry at what Batten Disease had done to his sister and she said “he was grieving the sister he had lost”.<br><br>*(Siblings mental health is another addition to the mental toll this take on parents).*<br><br>I will never forget one Christmas Eve when we would all go outside into the garden to throw reindeer dust on the grass. We thought it was lovely but it hit our son that his sister would never walk on the grass and throw the dust herself.<br>We put Christmas hats on and he was so upset again because he said how sad he felt for his sister and how he wishes she could understand more and get more involved as she was in a wheelchair and relied on us for everything. We assured him that she didn’t have to speak to understand so she was aware of what was happening and what we were talking about. I told him that she knew she was surrounded by love and that that was our job - to let her know and *feel* how much we adored her.<br><br>Another vivid memory that is forever engrained in my mind was one year on our wedding anniversary, we thought it would be nice to watch our wedding video together as a family. Our son turned to us half way through and said “Are wedding video’s meant to make you cry?”.<br><br>We said no sweetheart, why do you ask that?<br><br>To which he explained it was so sad looking at what his sister used to be like, running, laughing, getting into mischief in the video and how he wished she was still like that.<br>The rest of the evening was filled with very deep and sad conversations about how we wished more than anything we could change things, for his sister not to have battens and to be able to walk. But we told him that we have to channel our energies into what we can have an impact on.<br>We would all be crying all day every day if we lived our lives thinking of how cruel and horrid battens is and what it had taken from he, but that will not help her or us. We needed to try to focus on showering her with so much love which was something we could all do. Batten’s cannot take away the love we have for each other and she needs us to show her love every day. |

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| | I can't imagine watching your sister decline slowly over years and then looking at your other little sister with the obvious thoughts of will the same happen to her. The anxiety and worry this must be placing on him is so sad to imagine.<br><br>Thankfully the early intervention of treatment forour youngest daughter means she is walking a very different path so we just take things a day at a time and don't look into the future as we cannot control that, nor can we predict what the future for nour youngest daughter will look like as there has never been a child who started treatment as young as our daughter so we have nothing to compare against. Again for an older sibling, the weight of this uncertainty must be heavy.<br>We have hope in our hearts for a long and healthy future for our youngest daughter….but her future all depends on this continuation of her treatment.<br><br>Tragically our darling daughter passed away on October last year.<br>*An important point I would like to bring to the committee's attention is that we would to state that our daughter did not pass away due to Batten Disease. She had severe complications following a chest infection after covid, then unfortunately caught a secondary infection. Batten Disease was noted on the records but it was because it was a contributory factor in terms of her being compromised and more vulnerable. We fully expected to have many happy years ahead with her so her passing was a huge shock for us.* |
| 6. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? | **Delays**<br>Our oldest daughter was diagnosed in September 2016 after two and a half years from her first symptom was identified which was lack of speech.<br><br>The symptoms began with lack of speech, which despite intervention from speech and language therapist did not improve, which led us to see a Paediatrician who advised us that not speaking was the least of our worries and that he believed there was something bigger going on. He diagnosed our daughter with Global Development Delay on that first visit (her behaviours were that of a 18-20 month old and she was 3.5 yrs at this point) then a couple of days after that appointment, she had her first seizures, which led |

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| What was the impact of this on you and your family? | medical professions to agree there was something serious impacting her brain function. Then the regression in motor skills and mobility became apparent but we had no idea of the cause and just thought she needed a little help or she was perhaps tired.<br><br>The symptoms mounted and finally, after our insistence that there was something not right and further investigations were needed, we eventually received a diagnosis of CLN2 Batten Disease.<br><br>During that time our daughter lost skills which she would never get back.<br><br>From diagnosis in September 2016 there was a delay in beginning treatment of 4 months, as her first infusion was January 17. This was because she had to be assessed before she was given one of the last compassionate use spaces in Great Ormond Street which were so grateful for.<br><br>Our younger daughter was diagnosed far quicker as a result of her sister's genetic diagnosis although there was a delay in beginning treatment because she our so young she was outside of protocol (age 3) and all compassionate use spaces had gone. Thank fully after many discussions, the protocol was amended (age limit was reduced) to allow our daughter to join the Sibling Trial in Hamburg.<br><br>Other families have experienced long delays where their child has regressed and misdiagnosis during this time is common which further delays a diagnosis.<br><br>We are so glad the time from diagnosis to treatment happens much quicker now. |
| **Current treatment of the condition in the NHS (outside of the managed access agreement [MAA])** | |
| 7. What do you think of current treatments (if they exist) and care available on the NHS (outside of the managed | No other treatment exists so our children's lives and the lives of children who are diagnosed in the future, are dependent on a positive outcome.<br><br>This is the first and only available treatment for CLN2 Batten Disease which is why this appraisal process |

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| access agreement)? What are the things they do not do well enough? | is critical to the batten disease community.<br><br>Batten Disease is the most devasting condition but Cerliponase Alfa has been proven to significantly slow down the rate of regression and it is an approved treatment that many children around the world are benefitting from and I feel it is unethical for children in the UK to be denied access to the **only** treatment available for their condition that could ease their symptoms and give them a chance of a longer healthier life.<br><br>I hope that the committee can see how the key uncertainties expressed during the appraisal process of clinical effectiveness and cost efficiency have been successfully resolved. |
| 8. Is there an unmet need for patients with this condition? | An unmet need for patients with Batten Disease is the lack of a viable treatment to prevent vision loss.<br><br>Although both of our daughters are classed as 'A-Typical' for their vision, this is most definitely an unmet need for batten patients.<br><br>Our oldest daughter was 11yrs old and still had incredible vision (her vision quality was deemed too good to be considered for the recent eye treatment trial) and our youngest daughter is 8 years old, turning 9 in September and she has no vision issues at all but this is highly unusual and we do not know if her vision will remain stable in the future. |
| **What was the experience of the technology during the managed access agreement [MAA]?** | |
| 9. What has been the experience of having access to the technology during the period of managed access? | Our youngest daughter began treatment in Hamburg on the Sibling Trial while our oldest daughter was in London accessing treatment on a compassionate use basis.<br>Both transferred to the MAA and we continue to travel which was something we accepted and we would travel anywhere in the world if it meant our daughters would have access to treatment.<br><br>We are grateful for the quality of life that Cerliponase Alfa gave to our oldest daughter and we cannot express the different opportunities it has given to our youngest daughter so far and we hope this will continue. |

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| | However, the additional stress, anxiety, worry and time of having our children regularly expected to perform tasks and us having to complete assessments has been extremely taxing.<br><br>**In summary** – We were prepared to do whatever we needed to do to allow our daughters to have access to the treatment but the strain of the MAA was placing an extra unnecessary burden on parents and did not actually provide an accurate and true reflection of our children. |
| 10. How has the technology fitted in with other treatment and care for the condition? | Having the treatment in our home hospital (as opposed to GOSH) has helped us greatly with coordinating the girl's other appointments because we can ask the relevant consultants to come up and see us on the ward which has been working wonderfully well. Our oldest daughter had regular botox injections which were always carried out on infusion days for example.<br>As our younger daughter was diagnosed and had access to treatment so young, she does not require any additional treatment which is a testament at nearly age 9 yr she only requires Cerliponase Alfa alongside her epilepsy medicine. |
| 11. Describe how receiving the technology has impacted everyday life. Has it had an impact on what carers experience? How? | From a practical, logistical perspective, the technology has impacted our lives by us having to attend hospital every two weeks for the last 7 years so our lives have been planned around infusion days.<br>From a personal perspective the technology has impacted our lives by giving us our lives back and having such a positive settling impact on our daughter.<br>Knowing that our two daughters were receiving treatment that was proven to significantly slow down the progression of the disease, gave us hope as parents for a longer healthier life for our girls but the actual impact on our daughters health has been nothing short of miraculous.<br><br>Treatment has allowed us to be confident to travel and give our daughters as many opportunities as possible.<br><br>Our oldest daughter was a little miracle and the strongest little girl you could meet, she got to see the world, she swam with dolphins in Dubai, went to the top of the Bhurj Khalifa, swam in the Turkish sea, visited Santa in Lapland, was blessed by his Holiness the Pope, walked up the Spanish steps in Rome, visited Disneyland Paris and met so many princesses! |

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| | We did this to create magical memories as a family, we wanted to show her the world and let her experience as much as we could and she never missed out. We could never have done that without treatment having such a hugely positive impact on her health and wellbeing.<br><br>Our youngest daughter is our other miracle which I know you will be aware of as she is referenced in worldwide discussions as an example of how transformative Cerliponase Alfa is. She was the youngest child in the world to ever receive Cerliponase Alfa and this is what is giving her……..<br><br>Our daughter is 8 years old, is walking, running, climbing, goes up and down stairs completely independently swinging, scooting, attends ballet class, has a fantastic memory, it fully toilet trained and self sufficient in personal care and dressing / undressing herself. Her humour is amazing, she is witty, wild and has more energy than our entire family put together! She loves play parks and can navigate tricky equipment, she loves being outdoors, loves collecting sticks and leaves, she loves the beach. She has a great appetite, she is loving and emotionally intelligent, always mindful of people's moods and feelings and showing compassion and care to anyone she sees as upset or unhappy.<br><br>She loves school, can write her name, remembers storylines and predicts what is coming, telling you the story before you've turned the page!<br><br>If you met her, you would never know she had Batten Disease. The only reason our youngest daughter is doing so well because she was diagnosed so young and then crucially, she had access to treatment so young.<br>In comparison, when our oldest daughter was the same age, she had not spoken a word, she was tube fed, couldn't walk by herself and was dependant on us for every aspect of her personal care<br><br>Our youngest daughter is living proof that Cerliponase Alfa works and that if given early enough, it can change the course of this disease. She is re-writing the course of this disease and is bringing hope to others. |

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| | We have had the unique viewpoint of seeing the difference an earlier diagnosis can make in our two daughters. Our youngest daughter used to call her older sister her “baby sister” despite being 3 years younger because she saw how much care and help her sister needed. |
| 12. How easy or difficult is it to take/have the treatment? How does this impact you and your family (for example, travel or how the treatment is received? | When we used to travel to Germany and London, it was a huge burden, but as I said in an earlier answer, we would travel anywhere in the world. But compared to the typical family routine it was far from normal. Our son was only 6 years old at the time we began taking the girls for treatment. My mother in law would travelled 2.5 hours each way to take care of our son for us because we wanted to keep a consistent routine to try and provide him with a sense of security.<br>We would be heading out of the door to our son crying, begging us not to go and asking “why are you leaving me?”. It was an awful time in our lives but we had no option.<br><br>We began by one week taking our youngest to Germany, then our oldest daughter to London the next but we soon stopped that because we felt we were never having time at home and were packing our bags to leave too often which was very unsettling for our so. We then split and my husband would take our youngest to Germany and I would take our oldest daughter to London. The girls would get the same infusion on the same day, but in different countries.<br><br>We eventually managed to get our daughters treated together in GOSH then we achieved our ultimate goal of bringing treatment to our local hospital which has absolutely transformed our lives.<br><br>From flying to Germany, to trains & stays in London over 2 days to now just being a 15-20minute drive from home to the ward.<br><br>It is amazing and we are so proud that we managed to make that a reality and that now families from our region never have to face the stress of travelling to London. Having treatment in a local hospital not only alleviates the burden of travel but it makes everything feel more comfortable and manageable. You feel safe and secure that you are in a familiar place close to where you live.<br>Our local hospital is the Great North Children’s Hospital at The Royal Victoria Infirmary in Newcastle and we have been going there for years since our early health concerns were first raised with our oldest daughter so feeling familiarity and knowing the doctors and nurses makes a huge difference because we feel like you are home from home. |

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| 13. What place do you think the technology has in future treatment and care? | As this is the first and only approved treatment, Cerliponase Alfa is a lifeline for families so it should be placed firmly in the position of a long term treatment that is made available for all children with CLN2.<br><br>The advantages are it is giving our children a longer healthier life. It is giving families more quality time with their children. |
| **Advantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])** | |
| 14. What do you think are the advantages of the treatment? Consider the impact on everyday life and anything you described in the 'living with the condition' section. | The advantages of Cerliponase Alfa are it is saving our youngest daughter's abilities and saving her life. She is gaining skills and building the most wonderful relationships which is an absolute joy to see. She is doing things we never got to see our older daughter do.<br><br>She is developing and doing amazing. It was transformative for our oldest daughter and allowed us to have so many years of quality family time.<br><br>Cerliponase Alfa changed our daughters life. It was transformative and gave her an incredible quality of life, she had a life full of adventures, beautiful relationships, amazing experiences and fun. Only a few weeks before she passed, we were enjoying a beautiful holiday in Turkey and she was swimming in the Mediterranean sea.<br><br>We would never have been able to take her on holiday if it wasn't for the treatment that was keeping her so well.<br>Children of our oldest daughters age who were not on treatment were very sadly in palliative care state or had heartbreakingly passed away.<br><br>Our daughter was enjoying full time schooling, enjoying the hydrotherapy pool – she was able to enjoy so many things because of treatment. She was doing so well and never required any medications for sleeping, she never required over night oxygen or monitoring or intervention, she was doing so well for her age with this condition – because of Cerliponase Alfa. |

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| | We believed with all of our hearts that we would have had many more years to come with our oldest daughter. |
| **Disadvantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])** | |
| 15. What do you think are the disadvantages of the technology? Consider the impact on everyday life and anything you described in the 'living with the condition' section. | A disadvantage for some families is the difficulties of travelling to a treatment centre.<br><br>As our youngest daughter is getting older, she is becoming much more aware of the restrictions of the infusions and she will often say "I don't want my needles" or "I want to be free" (when she is hooked up for the start of the 4 hours infusion). She understands she needs the treatment and she will tell you "I need my needles to keep me healthy so I can walk and run and talk".<br>If she says she doesn't want to have her needles, we always tell you, you need your medicine to keep you healthy so you can do all of the amazing things you do now like, walking, talking and playing with your friends. She often replies with "but I'm ok" and we then say "yes you are, but that is because you have your medicine". |
| 16. Are there any side effects? What are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? | We have not experienced side affects in the past 5years however our youngest daughter did experience a short lived reaction. She had a temperature and was sick so we began premedication to prevent this. It worked instantly and the side effects disappeared.<br>Apart from that short period, we have personally had no side effects with either of our daughters.<br><br>The aspects of the condition that the treatment does not help with is vision loss however in our personal experience, both of our daughters had amazing eyesight at ages 11 and 8. The doctors cannot explain this but it could be that residual amounts of Cerliponase Alfa are reaching the retina – we do not know. Also, from our personal experience Cerliponase Alfa has not had any impact on our daughters' seizures and this continues to be a difficult symptom for us to manage, however, as noted in the BDFA submission, many families have confirmed that treatment has had a hugely positive effect on their child's seizures which is brilliant. |
| **What was measured during the managed access agreement [MAA]?** | |

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| 17. Thinking about the things that got measured during the period of the managed access agreement (MAA), do you think that all the things that were important were measured?<br><br>Please list what they were and why they were important (or unimportant) | I know I am not alone in my feelings and views on this topic (as you will read are those of other many other parents as documented in the BDFA submission) the assessments were incredibly stressful for parents and because of the reasons I will note below, were inadequate in capturing a true reflection of the child, therefore they did not provide a balanced assessment of where the child is and how they are.<br><br>**Important.**<br>MRI, ECG were important, relevant clinical measures which provide clear objective insight into the clinical state of the children's brain and possible atrophy and heart function are easily detected. The ECG assessment is painless and relatively quick which is a positive. Putting children under sedation for MRI is not ideal but understandably needed in some cases.<br><br>**Unimportant**<br><br>***Opthalmology*** testing was incredibly stressful and as Cerliponase Alfa is known not to effect or improve vision, I feel this assessment was not relevant and only caused the children and parent unnecessary stress. The actual testing was really intense and I still remember the distress that these tests caused myself and my children.<br><br>**EEG –** Given that Cerliponase Alfa was never expected to effect seizures, this would be an assessment that could have been omitted. Perhaps only being done is parents saw an increase in seizures and wanted reassurance or a more up to date analysis of their brain activity.<br><br>***Pfhycology*** assessments in particular placed an incredible amount of unnecessary anxiety on parents as more often than not, the children were either tired after an infusion, tired from travelling, or stressed because it was a clinical environment with people they do not know or feel comfortable with. Then the underlying pressure of hoping that your child would 'perform' in this tiny window of their life while parents are fully aware of the fact that the doctors and assessors were not seeing their child as they normally are. The nature of how prescribed the questions were was hugely frustrating because some of the language was not what we would use at home therefore our child would not be able to answer the question. I would dread the assessments because I was not allowed to interject or support my child for example the way a |

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| | question was delivered was not how my child would understand it, but if I was able to replace one word, it could have made all the difference and I know she would have been able to answer.<br><br>The telephone questionnaires with Rare Disease Partnership (Peds QL etc) were very upsetting for us relating to our oldest daughter and for families whose children had progressed in the disease and had lost many of their abilities.<br><br>The assessments could be triggering and upsetting because the line of questioning was not always relevant to the skill / ability level of the child. If you answer 'no' to the question "Is your child able to walk".....then you would not want to continue a line of questioning that is relating to other aspects of your child's mobility.<br><br>The question were open to interpretation and could be viewed as subjective "how well is your child today between 1-100?"<br><br>I have heard the assessments being referred to as 'torture' by families who found the level of sensitive questioning so upsetting, because you are forced to be reminded and confirm how many things you're child can no longer do. |
| 18. Were there things that were not measured but are important to you? If there were, please list what they were and why they were important. | **Quality of life should not be measured nor is it determined by the number of steps a child can take or if they can count to 10 or if they have medical intervention to support their health.**<br><br>What was missing was true, genuine, real world data which captured in the child's real quality of life.<br><br>The quality of someone's life could not possibly be captured through clinical assessments and parent questionnaires alone.<br><br>The assessments failed to capture real world data and were far too prescribed to allow for individuality or personalities to shine through - two traits which are hugely insightful into the child's development. |

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| | A far more accurate and useful way of capturing the impact of Cerliponase Alfa would have been to allow parents and schools to record their child in their day to day life at home, their achievements at school, participating in their favourite games, hobbies or activities, watching them interact with family and friends in the safety and comfort of their home and familiar school environment.<br><br>Our children's behaviour and abilities should not be contorted into a box for the purpose of achieving quantifiable results or scores. I strongly feel that there needs to be a more holistic and children centred approach to gathering 'real world' evidence to support the effectiveness of a treatment.<br><br>Our children could spend just as much time with their teachers as they do at home so having the input of external professionals should have automatically been used in the assessment process.<br><br>Everything rested on the child performing on that day. In that moment. A moment where they were not in their normal surroundings where they could be safe and comfortable and florish in their surroundings and really show people what their life outside of hospital looked like and how rich their lives were.<br><br>There have been concerns with assessments that require the child to have a significantly good level of vision so those with vision loss were not being accurately assessed. They may have the cognitive ability to answer the questions, but they could not see the objects for example, to be able to answer correctly. So it was an untrue reflection of the child's understanding, as opposed to the vision loss impairing their ability to complete assessments. |
| **Patient population (including experience during the managed access agreement [MAA])** | |
| 19. Are there any groups of patients who might benefit more or less from the | I feel very strongly that every child deserves access to a treatment that has the potential to help manage symptoms, extend their life, give the child a chance of enjoying precious time with their family and friends, |

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| treatment than others? If so, please describe them and explain why. | give them opportunities to experience adventures and most importantly, quite simply, it is giving the child a chance to live, to be here, to be loved and sharing their love with others.<br><br>Quality of life should not be measured nor is it determined by the number of steps a child can take or if they can count to 10 or if they have medical intervention to support their health.<br><br>My husband and I are in the unique position of being able to offer a perspective of what it is like to have two children with the same condition, both accessing treatment but both at completely difference stages of the disease because of the age at which they were diagnosed. They are both very different and had very different needs but they both benefited greatly from the treatment and both equally deserved the chance at a healthier life which Cerliponase Alfa gave them and continues to give our youngest daughter.<br><br>Our two daughters have been having treatment for 7yrs so we have watched the changes in our oldest daughter at the same time as celebrating the achievements and milestones of our youngest daughter. Their journey's could not have been more different but they BOTH deserved to be on treatment because it was preserving both of their lives and it gave us more quality time with our oldest daughter than we would have had without treatment without any invasive interventions that would have limited her ability to experience life to the full.<br><br>I do acknowledge that the children who are diagnosed at a pre-symptomatic stage will have the opportunity to not only retain skills but also attain new skills like in the case of our youngest daughter who |

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| | if you met her, would amaze you in what she is able to do and you would never know she had the condition.<br><br>But and this is very important to make clear, this does not mean children who are further progressed in the condition should be denied access to a treatment that could be transformative to them.<br><br>Our oldest daughter was non verbal, she was in a wheelchair, she was tube feb, she had other complex health issues which required other medicines and interventions, she was full dependant on us for every aspect of her life but my goodness she had an amazing fulfilling quality of life! She attended full time school, she was loved and adored by everyone she met.<br><br>Just because she couldn't walk or talk is in no way a reflection of her quality of life. She adapted to her changing needs and she was always happy. Having her in our lives was a blessing and we have Cerliponase Alfa to thank for helping her to live her life.<br><br>**In conclusion**<br><br>Regardless of time of diagnosis, the treatment is effective. Clearly the earlier the treatment is given impacts how transformative it can be. |
| **Equality** | |
| 20. Are there any potential equality issues that should be | **I have no comment to make to this question.** |

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| taken into account when considering this condition and the treatment? | |
| **Other issues** | |
| 21. Are there any other issues that you would like the committee to consider? | **Early Diagnosis.**<br><br>The age of diagnosis has a direct impact on the effectiveness of the treatment.<br><br>The treatment has proven to be much more effective when given to children as early as possible and our youngest daughter is one example of this as are other younger children around the world who started treatment at a much younger age.<br><br>Our youngest daughter, despite being 3 years younger, would refer to her big sister a her ‘baby sister” because she saw how much her sister need cared for, almost like you would a baby. A role reversal because of the age of diagnosis and access to treatment.<br><br>I appreciate that the following statement is not something that is in the committee’s remit at this juncture, however I do feel it is something that is pertinent to record with the hope of it being useful to the wider reach of some of the committee members who perhaps might be able to review this.<br><br>It is my view that much more needs to be done to diagnose children early in order to give them the best chance of living a longer healthier life. We need to find a way of capturing the early symptoms such as ‘unprovoked seizure’ or ‘language delays’ for example.<br><br>As the BDFA submission illustrates, these symptoms are the most common symptoms that present first. |

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| | Both of these symptoms as stand alone symptoms would perhaps be easily accepted as either 'a childhood convulsion' to be monitored and with language delays could be assumed that the majority of children have some language delays and the majority "will speak when they are ready" or "when they start school they will come on leaps and bounds".<br><br>But…..instead of these being separate stand alone symptoms, we need to educate the medical professions to take action and order tests if children are experiencing two or more symptoms which could be early indicators of Battens.<br>In our case, the first concern was our daughter not speaking at 2yrs old. Still no speech at 3yrs old. Then came a seizure. Diagnosed with Global Developmental Delay. Then her mobility began to change. Then 2.5yrs after the initial concern, following months and months of our insistence that something was not right, we received the Batten Disease diagnosis when she was 4.5yrs old. By this point she had lost skills she would never get back and the brain atrophy had begun. As it was genetic, our daughter was diagnosed at 15months old in comparison.<br><br>**Newborn Screening**<br><br>The optimum stage for diagnosis would be at the newborn screening phase given that there is a treatment available which has been proven to be affective for CLN2.<br>Which leads me to share my observation……..<br><br>Having only 9 conditions on the UK newborn screening panel is dismal given that we celebrate being world leaders in genomics, with access to the most advanced associated technologies and incredible resources in that field.<br>Compare that number (9) to other European countries like Italy and Iceland who screen for over 40 and then Slovakia and Hungary screening for 20+.<br><br>It highlights how far behind we are in such a hugely important area and I feel very strongly that this needs to be reviewed and the processes for adding conditions to be considered for screening to be simplified. |

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| | **Innovative Medicine Fund**<br>It is saddening that this fund is not able to help the batten community at this time as the introduction of it, following the success of the Cancer Drugs Fund, is exactly the type of help we need to bring Cerliponase Alfa to patients. |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

# Highly Specialised Technology

# Guidance review following a period of managed access

# Patient expert statement

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

| **About you** | |
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| 1.Your name | **Mrs Lucy Carroll** |

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| 2. Are you (please tick all that apply): | ☐ a patient with the condition?<br>☒ a career of a patient with the condition?<br>☐ other (please specify): |
| 3. Did your nominating organisation submit a submission? | ☒ yes, they did<br>☐ no, they didn't<br>☐ I don't know |
| 4. How did you gather the information included in your statement? (please tick all that apply) | ☒ I have personal experience of the condition<br>☐ I have personal experience of the technology being appraised<br>☐ I have other relevant personal experience. Please specify what other experience:<br>☐ I am drawing on others' experiences. Please specify how this information was gathered: |
| **Living with the condition** | |
| 5. What is it like to live with the condition? Consider<br>• the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your | We have two children with CLN2 Batten Disease. The disease does affect every aspect of our lives however it does not define who we are as a family.<br>Myself and my husband are now full-time carers to our children, whilst we both worked hard for our careers, we feel privileged to be able to be at home and care for all of our children. We have five children in total.<br>We do our very best not to let the impact of the disease affect the lives of our other children. We encourage them to participate in after school activities, we always ensure that one of us is always there for when they need us. This can sometimes put extra strain on the other parent who is left caring for two complex children however this is a choice that we have made as parents. We have been offered carers to help us, but we have chosen to care for our children ourselves. We are lucky to have a strong network of family and friends.<br>The biggest strain on the family is financial impact, this is due to being unable to work due to the complex needs of our children and that the benefit system for families with children with disabilities does sadly not meet our financial needs. Families with |

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| home, financial impact, relationships and social life).<br><br>• if you are the parent of an affected child, include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?<br><br>• what carers experience when caring for someone with the condition | children with CLN2 Batten Disease often find that they have to self-fund equipment and therapies that their children need due to them being unavailable on the NHS service or simply because the wait for these services is so long.<br><br>Adaptations to the home can often be financially challenging, although families can apply for grants these do not always cover the costs. Sometimes it is impossible for adaptations to take place and therefore families may need to move. This can result in having to leave the area and away from their support network.<br><br>Personally, we were able to adapt our home however we had to move ourselves and four small children into a temporary home whilst these adaptations took place.<br><br>A social life for a family like ours depends on how much support you have from family and friends; we have found that leaving our daughter is far easier than leaving our son who has more complex care needs. A Children's Hospice offers respite for families but this service is not for everyone.<br><br>There is often lots of lifting and bending which impacts on our physical health so it is of great importance that we keep ourselves fit and that we have the correct equipment in our home for example hoists and a lift to limit the physical strain on our bodies.<br><br>Our daughter who was diagnosed at a much younger age to our son and therefore gained easier access to treatment is able to attend full time education. She was able to attend mainstream school until the age of eight. We then decided to move her to a special school where she has daily access to therapy.<br><br>Our daughter has wonderful friendships with children both within the school setting and outside of school. She is able to attend after school clubs, such as gymnastic sessions. Here is she able to mix with neurotypical children who adore her. This allows her to build her confidence, physical, social and emotional skills as she is able to learn through others.<br><br>We also believe that our daughter is also teaching the children around her the importance of inclusion and how in every walk of life no one person is the same.<br><br>Our son no longer attends school, this decision is a personal decision due to the behaviour of certain individuals towards our son whilst he attended a mainstream school. Sadly, not everyone is kind to those who are deemed as different to the norm and it was because of this we feel extremely protective of our son and so now he remains at home in our care. He does however have two incredible teachers from outreach who come to the home twice a week and engage with him through, play and therapy. We are lucky to be a big family so he has plenty of opportunity to socialise with his siblings, cousins and family friends.<br><br>We feel it is important to remain as a united family and therefore we often attend events, outings, football matches all together. We are however finding this harder the older our two children with the disease become simply due to the lack of disabled facilities there are in the UK. For example, the lack of disabled change and hoist make it sometimes impossible to go on a full day out and we find ourselves having to plan our outings to where these facilities are available. To reiterate this is not due to the disease but rather the lack of understanding from the world around us that basic needs should be met regardless of disabilities. |

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| | Siblings are massively impacted, everything we feel as parents they are also feeling. For older siblings they too are watching as their once healthy sibling is robbed of their abilities and experiences trauma in the most horrific ways. They are now not only just children but they too become caregivers, they become experts in the disease and they themselves experience trauma by what they are witness too.<br><br>It would be naïve to think that this will not affect them, however with support we have found personally that siblings do in fact become extremely strong, resilient, caring and inspirational in their own right.<br><br>Younger siblings are born into a medical world, they know no different and whilst they may ask questions, as they grow their understanding of the disease and of the world is very different.<br><br>Siblings are full of love for one another, the bond is unique and we have often found that siblings will always put the needs of the poorly siblings before their own without question.<br><br>Siblings need a healthy network of emotional support both in and outside of the home, they need to be able to have the space just to be themselves, have a place where they can forget their worries but also a space where they are able to express their feelings without judgement.<br><br>Parents often feel like they are constantly fighting for support, equipment and the basic needs for their children. This is often hard both mentally and physically. Again, this is not the child or even the disease its self but rather the systems that have been put in place. For example, only today we went to place an order for our sons' pads, something which should be simple but because he was due a review he had been discharged from the service. A child with this type of condition is sadly not going to improve or get better therefore a review like this is not needed. As a parent I then had to spend the afternoon chasing professionals in order to explain our situation and get our son's account reactivated. Unfortunately, occurrences such as this are not rare. |
| 6. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this on you and your family? | Relatively speaking our diagnosis was quick compared to others, however we do feel that there could have been an improvement with the speed of diagnosis. Our concerns about a speech delay and clumsiness were dismissed for quite some time by professionals. It was only when our son started experiencing seizures a year later did things start moving forwards. However, this was not by our local hospital. After our son experienced a seizure in a park close to our home he was taken via ambulance to our local hospital. Here whilst still unconscious we were informed there would be quite a wait to see a doctor. This is when we made the decision to take our son out of A and E and to another hospital. This was a specialised hospital so once we were able to explain our sons' symptoms, we felt we were being taken more seriously. After a few weeks for tests such as EEGs, ECGs, CT scans and MRI scans to be carried out we met with a neurologist who ordered genetic testing. We have since found out that this neurologist had in fact already seen children with Batten Disease so knew which tests were needed. We believe if it was not for the experience of this neurologist then the diagnosis could have taken longer. |

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| | Being given our sons diagnosis was obviously the worst day of our lives. However, if we take away the emotional side of that situation it still could not have gone any worse.<br><br>The diagnosis itself was not explained very clearly, we were given a A5 piece of paper with some information on, our son was also present in the room at the time of diagnosis, it's important to note that at this time his understanding was in line for his age (four years old). There were four doctors in the room and a nurse, some showed no emotion and others became quite upset themselves.<br><br>When we asked if there were any trials going on in this country or elsewhere in the world, we were told no. We later learnt through our own research that this was not true and there was in fact a trial taking place in London and in other centres across the world. We were also not told that the disease was genetic and that our other three children at the time could also have the disease.<br><br>We felt very alone and isolated. We had to do all the research on this disease and the currently trials ourselves. We reached out to two specialised doctors in London who agreed to help and support us. We were not referred or directed to these doctors by the team who diagnosed our son.<br><br>We also had to ask for genetic testing on our other three children. This was not something offered too us. These tests confirmed that our youngster daughter at the time also had the disease, she was just two years old.<br><br>This was an extremely emotional and upsetting time for us as a family. The lack of support and understanding meant that we as parents had to take time away from our children to do our own research in order to support them better. We should have been allowed time to be upset, to grieve and to spend that precious time with our child, time which we will never get back. |
| **Current treatment of the condition in the NHS (outside of the managed access agreement [MAA])** | |
| 7. What do you think of current treatments (if they exist) and care available on the NHS (outside of the managed access agreement)? What are the things they do not do well enough? | Sadly, there are no other treatments for CLN2 Batten disease only the management of symptoms. The care which children and families receive differs from area to area, we often call it a postcode lottery.<br><br>Assessments are often needed for equipment; these assessments can often take time to set up. Professionals then have to take the needs of the child to panel to apply for funding. If agreed orders can then be placed. Often this process can take months and during this time the child and families are left to struggle.<br>All families of children with complex needs such as those with CLN2 Batten Disease are entitled to a Disability Social Worker for support however families are not always told this and often the social team will try to downgrade the families to decrease their workload. There is also often a lack of understanding around the disease and the support that is needed due to its rarity. Managing the symptoms of the disease can be tricky, we believe it is important that families and children with this disease develop a close positive relationship with the appropriate professionals. All professionals and the family must work together ensuring that the child is managed under the same understanding and that medication changes or changes to care is done as a team with clear explanations given to parents. |

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| 8. Is there an unmet need for patients with this condition? | A clear treatment plan under the NHS.<br>A treatment for the loss of vision.<br>A pathway to support children and families with vision loss.<br>Hope is for there to one day be a cure for this disease. |
| **What was the experience of the technology during the managed access agreement [MAA]?** | |
| 9. What has been the experience of having access to the technology during the period of managed access? | When the MAA first started, we were receiving treatment at Great Ormond Street Hospital, (GOSH) As we were already on the treatment before the MAA the only thing to change were the assessments which are needed to collect data.<br>Half way through the MAA we moved our children's treatment to Manchester Children's Hospital. This meant that the treatment became much closer to home.<br>We had to get used to a new team of professionals looking after our children. However, everyone involved where so lovely and soon became our second family just as the team at GOSH had been for many years.<br>At the time we moved the treatment to Manchester Children's Hospital our sons access device in his brain broke. We had learnt that at the time two children one in the US and another in Australia had chest ports fitted. These types of ports seemed to be lasting much longer and from speaking to the parents it seemed they were also more comfortable for the children and held in place a lot easier.<br>We approached one of the surgeons in Manchester along with the information about the chest ports from the US and Australian surgeons. We asked if this surgery could be carried out on our son, this would be a first for the UK.<br>The surgeon agreed and we are very proud to say it was a huge success. We are now two years post-surgery; we have experienced no issues. Other patients are now offered this route of access as standard at Manchester Children's Hospital. We also decided to have the same surgery for our daughter. |
| 10. How has the technology fitted in with other treatment and care for the condition? | Every other aspect of care is planned around brain infusion day, this is understood by all professionals and we have never had any issues.<br>We are very lucky that both at Great Ormond Street Hospital, London and at The Royal Manchester Children's Hospital our team arrange appointments and assessments to take place on the same day as our infusions to help limit our visits into the hospital.<br>We are also able to speak with our neurologist, metabolic consultant and therapists regarding any concerns during our infusion day. |

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| 11. Describe how receiving the technology has impacted everyday life. Has it had an impact on what carers experience? How? | Since receiving the treatment hospital admissions have reduced massively. Our children's health has remained relevantly stable allowing us to concentrate on spending quality time with all of our children, creating experiences and making memories.<br><br>We have to be aware that our children do have a device within their brain and their chest but this does not affect their everyday life. They are able to join in with activities as normal, attend school, go swimming they are also able to fly. |
| 12. How easy or difficult is it to take/have the treatment? How does this impact you and your family (for example, travel or how the treatment is received? | When our children first started receiving the treatment back in 2016 under compassionate use, we had to travel from Manchester to London via train not a very easy task with two children, a wheelchair, a buggy and suitcases. We would stay over night in London, attend Great Ormond Street Hospital for treatment for the next day for a full day where our children would be observed continuously whilst receiving their brain infusions. We would then stay over on the hospital ward for observations. We would then return home the next day via the train.<br><br>We would have to leave our other two children aged seven and eight with family members for three days every other week.<br><br>It was a hard period, but one which grew into our routine and soon became our normal.<br><br>During the Covid lockdowns we had to drive from Manchester to London, we would leave our home at 2am and make the five-hour car journey to Great Ormond Street Hospital in London. We would then spend the whole day in one room of the hospital for our children's treatment, we would then leave and make the five-hour car journey home all in one day.<br><br>At this time, we had also just had a baby who was still a new-born due to the hospital regulations she was unable to come into the hospital with us, therefore we had to leave our new-born along with our two older sons with family members.<br><br>Half way through the MAA we moved the treatment from Great Ormond Street Hospital, London to The Royal Manchester Children's Hospital.<br><br>This has made our lives so much easier. The hospital is now only a forty-minute drive from our home. We now leave the house at ten in the morning and we are home in time for tea time.<br><br>It also means that we are around on treatment days for our other children if they need us for any reason as we are close enough for one of us to nip out of the hospital.<br><br>We have been very lucky we hope both our children have responded to having to be in hospital for treatment. Our daughter started receiving treatment at the age of three, she knows no different. She enjoys going into the hospital. She has a fantastic relationship with the nurses and the doctors who care for her. Neither of our children become upset when it is time to access their devices. We do however believe that it has become easier for us and for those accessing the device now that the device is in the chest. The child does no longer have to be perfectly still, they are less likely to do a sudden big movement when being access and they have more freedom to move during their infusion.<br><br>It is also easier to clean and secure. |

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| 13. What place do you think the technology has in future treatment and care? | It is paramount that this treatment becomes available on the NHS for children with CLN2 Batten Disease. This currently the only treatment which has been proven to slow down the progression of the disease and improve quality of life not only for the child battling the disease but also their family as a whole.<br>Without this treatment children suffer daily at the hands of this disease. We are personally in a very unique situation where our children were diagnosed before there was access to a treatment.<br>Whilst we were fighting for our children to gain access to enzyme replacement therapy (ERT) our son deteriorated very quickly, some of his symptoms where horrific and at times it was unbearable to watch the amount of pain he had to injure.<br>Within weeks of starting enzyme therapy his symptoms improved and we even began to see parts of him return.<br>Our daughter's journey has been very different. She was able to start receiving treatment at a much younger age. She was three years old when she started treatment, our son was nearly six, because of this we have a direct compassion between the two.<br>The benefits of gaining access to treatment at a younger age are huge. We believe that new born screening is needed to ensure an early diagnosis and in turn early access to treatment. |
| **Advantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])** | |
| 14. What do you think are the advantages of the treatment? Consider the impact on everyday life and anything you described in the 'living with the condition' section. | This treatment has slowed down the progression of the disease in both of our children. Our children are now thirteen and eleven. Life expectancy is six to twelve years.<br>This treatment 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.<br>Since starting treatment in 2017 our daughter has experienced only one seizure which happened recently.<br>The need for many medications has been reduced and changes in medication may not be needed often.<br>Hospital admissions have been reduced and the need to call for the emergency services has also been reduced. When our son was diagnosed, we were calling for an ambulance a few times a week, this was a very upsetting time for our other children. Since starting treatment this has now turn into a rare occurrence.<br>Due to starting treatment at such a young age the symptoms of the disease were kept at bay for many years for our daughter, this allowed her to be a little girl. She attended mainstream school with her friends, she joined in with after school activities, |

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| | learnt like other children her own age and was simply able to be a child who had no medical problems. The disease did not start to impact our daughter until the age of eight.<br>The treatment has reduced the amount of care that is needed to be given to both our children. Despite our son being further along in the disease compared to our daughter he is relatively stable. Historically he should no longer be with us yet instead he is still able to have a wonderful quality of life. He requires limited medical intervention at home. He is able to come out on outings with us as family and is even able to travel aboard by aeroplane. He enjoys swimming and interacting with his family and friends. He has the most joyful smile and will laugh at anyone who is being 'naughty'.<br>Our daughter is now eleven years old; she too has a fantastic quality of life; she is still able to speak and can hold a conversation with both adults and children. She is able to eat orally, stand and walk with assistance and enjoys out of school activities. She recently placed first in a SEN international Gymnastics competition. Her knowledge, understanding and memory is incredible. Neither of our children show any signs of childhood dementia.<br>The treatment itself has its own routine. It is at the same time, on the same day for every treatment. This allows us to plan our lives around our infusion days without having to worry that the day may suddenly change. The team is the same each time we attend hospital which allows us and our children to build up a trusting relationship with those caring for our children.<br>This also allows us to build a consistent routine at home for our other three children. |
| **Disadvantages of the technology (treatment) (including those experienced through the managed access agreement [MAA])** | |
| 15. What do you think are the disadvantages of the technology? Consider the impact on everyday life and anything you described in the 'living with the condition' section. | We believe the biggest disadvantage of the treatment is that the treatment is unable to cross the blood brain barrier meaning children receiving the treatment will still lose their vision.<br>Vision loss impacts on the children massively. We truly believe that if our daughter still had her vision, she would still be on her feet.<br>At the time our daughter lost her vision she was still able to run around, we saw her confidence fade as her vision deteriorated until one day she refused to walk. It was not that she was unable but more that she was scared to do so.<br>We feel that there is a huge lack of support for families and children regarding the loss of vision. A pathway needs to be put in place to allow children and families to learn skills and coping mechanisms before the deterioration of vision loss starts.<br>We are aware of a number of trials taking place which we hope will show positive results in slowing/preventing the loss of vision.<br>Treatment centres are not always close to home, this can mean that families are having to travel and stay away from home. This can impact the family both emotionally and financially. However, this is now not as common due to more treatment centres opening. |
| 16. Are there any side effects? What are they, how many are there, are they long term or short term and what | Our son does not experience any side effects from the treatment. He has been having treatment for eight years.<br>Our daughter can experience extremely high temperatures after her infusion. She now has a steroid before her treatment and has not experienced this side effect for four years. |

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| impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? | Sometimes our children maybe tired the day after an infusion, we believe that this is due to an early start, along with a long day in hospital rather than the treatment itself.<br><br>As mentioned above the treatment seems to have limited positive impact on vision loss. A small amount of the drug must be getting across the blood brain barrier as our daughter's vision started to deteriorate at the age of eight compared to our son who was fully blind by the age of six years. |
| **What was measured during the managed access agreement [MAA]?** | |
| 17. Thinking about the things that got measured during the period of the managed access agreement (MAA), do you think that all the things that were important were measured?<br><br>Please list what they were and why they were important (or unimportant) | MRI Scans – important as these show changes in the brain over a twelve-month period.<br><br>EEG – unimportant to do standardly every six months. EEGs should be done when professionals deem it necessary. This maybe more or less than every six months.<br><br>Bloods – Important as this can show changes within the body that may not show to us outwardly.<br><br>Psychology assessment – Important, however should not be carried out in a hospital setting and real-world data should be used. Please see below.<br><br>Quality of life questionnaires – These are important as they are filled out by the parents, however the questions are dependents on how they are interpreted and some questions are not appropriate for patients with CLN2 batten Disease.<br><br>CLN2 Rating Scale – Depending on which centre patients attend this can be done by a different doctor each time, some patients are sometimes reviewed by a doctor that does not know their child.<br><br>ECG – Important.<br><br>Vision tests and OCTs – Important to a point but unnecessary once a child has severe vision loss. |
| 18. Were there things that were not measured but are important to you?<br><br>If there were, please list what they were and why they were important. | Real World data was not collected during the MAA. We believe that this type of data would have a huge impact on the findings.<br><br>Often the assessments that would take place in the hospital settings would be done at inappropriate times. Children would be tired; they would be placed in unfamiliar environments and be asked to perform in front of strangers.<br><br>Many times, during psychology assessments our children would be asked to demonstrate their understanding through objects which were not age appropriate nor of interest to them. We would also be in a room full of toys yet our children were expected to sit at a table and point at pictures when all they truly wanted to do was to get up and play with all the new and wonderful toys that were around them. These assessments were also carried out after our children had been confided in a hospital bed for four hours whilst having their brain infusion. |

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| | Real World data taken by parents, teaching professionals and therapists would show a child's true understanding and how the individual child performed and acted in familiar environments in everyday life alongside familiar people.<br><br>Professionals within a hospital setting are only acquiring a small snapshot of a child at that very moment in time. This is not enough to pass judgement on how a child is developing.<br><br>Up until recently the psychology assessments were not fit for purpose for those children with vision loss. For example, our daughter was able to recognise shapes, colours, letters and numbers. She was also started to attempt to write out her own name, her vision then deteriorated in-between her assessments meaning that when she was next assessed she could no longer do these things. Our daughter lost marks on the rating scale however the only reason she could no longer do these things was due to her vision loss and the fact she could no longer see what was in front of her. This was not accounted for at the time of the assessment. Therefore, this means that in our opinion inadequate data would have been acquired.<br><br>When we first started the MAA, our children had echocardiograms every twelve months. Part way through the MAA the was stopped. We believe that these assessments should have continued. During the previous NICE review concerns were raised over health of the organs as the children became older. These assessments could not only gather data but also pick up any potential early damage to the heart. For information our son, age thirteen has recently had an echocardiogram which was normal. |
| **Patient population (including experience during the managed access agreement [MAA])** | |
| 19. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why. | Every person with this disease deserves and has the right to access this treatment.<br><br>Quality of life should not be only determined by a person's ability to walk and talk.<br><br>Early diagnosis and early access to treatment is of extreme importance however this does not make patients with a later diagnosis any less worthy at a chance of life. |
| **Equality** | |
| 20. Are there any potential equality issues that should be taken into account when considering this condition and the treatment? | **N/A** |

| Other issues | |
|---|---|
| 21. Are there any other issues that you would like the committee to consider? | The negative impact of Covid on access to therapies and support. Families were left alone and isolated for many months. Children were unable to attend school or have access to therapies which where important to keep them stable and strong. |

Thank you for your time.

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NICE National Institute for Health and Care Excellence

# Highly Specialised Technology

# Guidance review following a period of managed access

# Clinical expert statement

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

| **About you** | |
|---|---|
| 1. Your name | **Dr Dipak Ram** |

| | |
|---|---|
| 2. Name of organisation | **Royal Manchester Children's Hospital, UK** |
| 3. Job title or position | **Consultant Paediatric Neurologist** |
| 4. Are you (please tick all that apply): | ☒ **an employee or representative of a healthcare professional organisation that represents clinicians?**<br>☒ **a specialist in the treatment of people with this condition?**<br>☐ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ **yes, I agree with it**<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |

| | |
|---|---|
| 6. Do you have a conflict of interest that you wish to declare[1]? | Nil |
| 7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☒ **yes** |
| **The aim of treatment for this condition** | |
| 8. What is the main aim of treatment? | To slow down progression of condition and to maintain motor skills and speech and language skills as much as possible and keep epilepsy under control |
| 9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by | 1. Maintenance of motor and oral skills<br>2. Reduction of seizure control by >50% compared to baseline and untreated cohort |

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

| | |
|---|---|
| x cm, or a reduction in disease activity by a certain amount.) | |
| 10. What are the benefits that you expect the technology to provide compared with routinely commissioned care? | Health benefits. Please delete as appropriate:<br><br>Increased survival Y<br><br>Increased time to progression Y<br><br>Improved QOL Y<br><br>Does the new technology provide other substantial health related benefits not included in the QALY calculation? Y – In patients treated early, the outcomes appear better and maintenance of mobility and seizure control is good. In those who started<br><br>Non-health benefits. Please delete as appropriate:<br><br>Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Unable to comment<br><br>Improved accessibility to patients Y, please explain: Less travel to single centre in UK now that there are multiple sites open<br><br>Implications for delivery of the NHS service Y, please explain: As more diagnosis made, there may be added pressure for beds and staff for fortnightly treatment |

| | |
|---|---|
| 11. Are there any recognised side effects of the technology? | No major issues apart from devices needing replacement in some patients.<br><br>Allergic reaction in some patients – managed with anti-allergy medications.<br><br>Possible risk of device infection but not seen in our cohort. |
| 12.Are there any important outcome data that were not collected during the managed access period? | Only generalised seizures were included in data collection but some patients may have troublesome jerks (smaller seizures) which are frequent and this is not captured in MAA. |
| 13. In your view, what is the unmet need for patients and healthcare professionals in this condition? | There is no clear objective stopping criteria for health professionals as current stopping criteria is also based on family questionnaire. |
| 14. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it | If patients are started on treatment early, they can benefit from this as they do not follow the natural history of the condition and hence less burden on healthcare compared to untreated cohort. |

| | |
|---|---|
| improve the way that current need is met? | |
| 15. Are there any groups of patients who might benefit more or less from the technology than others? | Younger patients who are diagnosed early and walking steadily seem to benefit more compared to those who are unsteady with their gait and diagnosed at a later stage. |
| **What is the expected place of the technology?** | |
| 16. How is the condition currently treated in the NHS?<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which? | Without this technology, the standard care of treatment is supportive care in a degenerative condition which is ultimately fatal. There are no clinical guidelines used but patients' symptoms are managed accordingly. |
| 17. Are there other clinical pathways used in England other than those recommended in the guideline? | Not aware of this |

| | |
|---|---|
| 18. Would the new technology require a change in the clinical pathway? | No |
| 19. Will the technology introduce new costs to the NHS or patients other than for the technology itself? | Not anything different to standard of care unless having an admission due to device requiring a change (admission and device cost etc) |
| 20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned?<br><br>If not, how would starting and stopping criteria be adapted? | Currently, the stopping criteria is not as objective. There are CLN rating scales to guide clinicians to discuss stopping treatment but QALY surveys from family may supercede these objective scales and patients may continue treatment indefinitely when their CLN scores are low. |
| **What was your experience of the technology during the managed access agreement [MAA]?** | |
| 21. What has been your experience of administering | Positive: The patients who are pre-symptomatic or have had early diagnosis have benefited particularly from this treatment. In general, most patients have benefited in terms of slowing disease progression and managing their seizures. |

| | |
|---|---|
| the technology during the period of the MAA? | Negative:Lack of objective stopping criteria – as outlined above |
| 22. Did any people decline treatment? What were their reasons why? | No |
| 23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA? | Most patients attended CLN clinics for their assessments and the MDT assessment has been helpful to score patients accurately |
| 24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How? | We would not do serial MRI and EEG in patients not on the MAA. |
| 25. Are there other points of learning arising from the period of the managed access | No |

| | |
|---|---|
| agreement that you would like considered? | |
| **Sources of evidence** | |
| 26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence? | No |
| **Topic-specific questions** | |
| **27. Key issue 6:**<br>• At what age are people currently diagnosed with CLN2?<br>• Which baseline distribution across health states best reflects that of people initiating treatment in clinical practice? (Distribution 1 - HS1: 50% HS2: 50%, Distribution 2 - HS1: 87.5% HS2: 12.5% or other)<br><br>*HS1 and HS2 = motor and language (ML) scores of 6 and 5 on the adapted version of the* | We are seeing more patients with ML scores of 5 and 6 in the past year due to earlier diagnosis. These patients are benefiting more from the patients.<br><br>Current age of diagnosis is about 3-4 years of age. Previously, the average was closer to 4 – 4.5 years, so things are improving. |

| | |
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| *four-domain Hamburg scale measure, the CLN2 clinical rating scale, which includes the motor and language domains of the scale and excludes the vision and seizure domains.*<br><br>• Are age and ML score distribution at diagnosis expected to change in the near future? If so, why? | |
| **28. Key issue 7:**<br>• What proportion of people that start treatment with a ML score of 6 would you expect to be "initial stabilisers"? (100%, 80% or other)<br>*Initial stabilisers = All remain in HS1 for the first 6 years in the model. Beyond 6 years, transitions to worse health states occur at half the rate of the transition probabilities applied to those who enter the model with a worse ML score.* | Agree with 100% for first 6 years followed by description provided with worse health state potentially occurring at half the rate |
| **29. Key issue 10**<br>• When does vision loss start for most people with CLN2, and by what age on average would people completely lose their vision? | Usually begins between 5-6 years of age in many and may lose vision by 7-9 years (some may still perceive shadows and lights and large objects) |

| | |
|---|---|
| • Do you expect cerliponase alfa to improve or stabilise vision loss in the long-term? | No – not intraventricular delivery |
| **30. Key issue 11:**<br>• In clinical practice, when would you expect cerliponase alfa to be discontinued?<br><br>• Would you expect a treatment effect to remain after discontinuation of cerliponase alfa? | When ML scores have deteriorated to 0-1, we would expect this to occur but due to MAA and family QALY service, this has been more challenging than anticipated.<br><br>Would expect some treatment effect to remain for potentially months after. |
| **Equality** | |
| 31. Are there any potential equality issues that should be taken into account when considering this treatment? | NO |

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# CONFIDENTIAL UNTIL PUBLISHED
# Addendum to the External Assessment Group Report

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]


**Produced by** CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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**Date completed** 05/06/2024

This addendum to the External Assessment Group Report (EAR) reports the applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC when excluding carer and sibling disutilities from the analyses reported in Section 6 of the EAR. These are shown in Table 1.

**Table 1 Cost-effectiveness threshold for each analysis in Section 6 of the EAR**

| | Scenarios | CE threshold £/QALY |
|---|---|---|
| **Company's base case** | Company's base case | £300,000 |
| **EAG Scenarios** | Scenario 1.1: Current clinical practice (HS1: 15%, HS2: 45%, HS3: 30%, HS4:10%; age 4.5 years) | £153,704 |
| | Scenario 1.2: Clinical practice in 5-year time HS1: 50%, HS2: 35%, HS3: 12.5%, HS4:2.5%; age 3.5 years) | £256,021 |
| | Scenario 1.3: As per original HST12 (HS1:50%, HS2: 50%; age 4 years) | £266,658 |
| | Scenario 2: 80% of patients in HS1 at model entrance are initial stabilisers | £300,000 |
| | Scenario 3.1: 100% progression multiplier for initial stabilisers | £244,498 |
| | Scenario 3.2: 75% progression multiplier for initial stabilisers | £289,840 |
| | Scenario 4: Backwards transitions to healthier states not allowed | £190,337 |
| | Scenario 5.1: Linear decline with age between 6 and 10 years old | £300,000 |
| | Scenario 5.2: as per original HST12 (driven by cumulative proportion of vision loss in the SoC) | £300,000 |
| | Scenario 6: Neuro-disability mortality included for HS6-9 | £300,000 |
| | Scenario 7: 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. | £300,000 |
| | Scenario 8.1: Carer and sibling disutilities for cerliponase alfa are the same as for the SoC values | £300,000 |
| | Scenario 8.2: Carer and sibling disutilities for cerliponase alfa correspond to 75% of the SoC values | £300,000 |
| | Scenario 9: Including ECG monitoring costs | £300,000 |
| | Scenario 10.1: 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 | £300,000 |
| | Scenario 10.2: Proportion of patients with progressive symptoms (other than seizures) is the same in both treatment group as from company's clinical experts for SoC | £300,000 |
| | Scenario 11: Including psychiatric/behavioural support costs | £300,000 |
| **EAG's preferred assumptions** | Company's base case + Baseline characteristics as per original HST12 | £266,658 |
| | Analysis 2 + 80% of patients in HS1 are initial stabilisers | £249,127 |
| | Analysis 3 + transition probabilities health state 1-7 informed by 'all patient dataset' | £150,524 |
| | Analysis 4 + Vision loss as per original HST12 | £143,946 |
| | Analysis 5 + Neuro-disability mortality applies to HS1-9 | £142,751 |
| | Analysis 6 + Treatment discontinuation at HS7 | £168,899 |
| | Analysis 7 + Including ECG costs | £168,899 |
| **EAG base case** | EAG base case: Analysis 8 + Including psychiatric/behavioural support costs | £168,899 |
| **EAG additional scenarios applied to EAG base case** | EAG base-case + Baseline characteristics as per company's base-case | £225,688 |
| | EAG base-case + Baseline characteristics as per clinical opinion of current practice in 5-year time | £166,108 |
| | EAG base-case + Transition probabilities health state 1-7 as per company's base-case | £263,818 |
| | EAG base case + Treatment discontinuation at HS6 as per company's base-case | £142,751 |
| | EAG base-case + Treatment independent health state utilities based on Gissen 2021 | £148,553 |
| | EAG base-case + Vision loss: age dependent and with linear decline until age of 10 | £171,443 |

Abbreviation: CA, cerliponase alfa; CE, cost-effectiveness; ECG, electrocardiography; HS, health state; HST, highly specialised technology; MAA, managed access agreement; SoC, standard of care.

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# Addendum 2 to the External Assessment Group Report

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]


**Produced by** CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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**Date completed** 06/06/2024

This second addendum to the External Assessment Group Report (EAR) reports a corrected version of Table 26 of the EAR. The company's "Source of utility values: MAA" scenario is corrected, as the estimates reported in Table 97 of response to clarification questions incorrectly reported these results; correct results are presented in Table 1.

**Table 1: Company scenario analysis results for cerliponase alfa (adapted from Tables 97, PfC response)**

| | Incremental costs | Incremental QALYs | ICER (£/QALY) | % change from base-case ICER |
|---|---|---|---|---|
| **Base case** | [redacted] | 17.35 | [redacted] | [redacted] |
| No treatment discontinuation | [redacted] | 17.86 | [redacted] | [redacted] |
| Starting distribution: Study 190-203 | [redacted] | 11.78 | [redacted] | [redacted] |
| Starting distribution: MAA (new patients) | [redacted] | 7.82 | [redacted] | [redacted] |
| Source of transitions: All patients | [redacted] | 14.27 | [redacted] | [redacted] |
| Source of transitions: All patients (piecewise at 6 months) | [redacted] | 22.86 | [redacted] | [redacted] |
| Duration of ML 6 stabilisation: 12 years | [redacted] | 18.52 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 75% | [redacted] | 19.54 | [redacted] | [redacted] |
| Reduction in transition probabilities (ML 6 stabilisers): 100% | [redacted] | 22.11 | [redacted] | [redacted] |
| **Source of utility values: MAA** | [redacted] | **16.20** | [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: Gissen 2021, treatment-independent utility values | [redacted] | 16.88 | [redacted] | [redacted] |
| Scenario: MAA (all patients), treatment-independent utility values | [redacted] | 15.03 | [redacted] | [redacted] |
| Scenario: Include testing costs | [redacted] | 17.35 | [redacted] | [redacted] |

Abbreviations: CE, cost-effectiveness, ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care

NICE National Institute for Health and Care Excellence

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]

27 June 2024

Dear Company,

Following the first committee meeting for the appraisal of cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) on 12 June 2024, the committee has requested further information to aid its decision-making.

The committee concluded that there was not sufficient evidence for deciding what the baseline distributions for the health states were. The committee felt that the EAG's and company's assumptions for baseline distribution health states were too optimistic, but it also felt that the distribution used in the EAG's clinical expert current clinical practice scenario was too conservative. The committee noted that the baseline distributions stated by one of the clinical experts at the meeting of 28.5% in HS1, 28.5% in HS2 and 42% in HS3 were plausible figures and could be considered in a scenario analysis.

The committee also concluded that using Study 190-203 for transition probabilities was unrealistic currently in the NHS and that using the pooled data was preferred. The committee acknowledged the impact of the covid pandemic on the MAA data and therefore requested seeing the pooled data excluding the MAA.

The committee has outlined additional analysis that it would like to see the company provide.

Health state distribution at model entry:

- The committee would like to see further analysis using data taken from current clinical practice that excludes patients where diagnosis or treatment initiation was delayed because of COVID-19.

Evidence source informing transition probabilities:

- The committee would like to see analysis that uses a dataset that pooled together data from Study 190-201/202 and Study 190-203.

Starting and stopping rules:

- The committee would like to see further analysis that considers the inclusion of starting and stopping rules into the model. Starting and stopping rules should be used to identify subgroups of individuals for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost effective.

Non-reference-case-analysis with background care costs removed:

The committee noted that section 4.4.16 of NICE's health technology evaluations: the manual (2022) states that 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 would like to see analysis with background care costs removed. The rationale for removing specific background care costs and any structural assumptions used in the analysis should be clearly documented.

Please consider all the committee's preferred assumptions in your analyses, as follows:

- The company's estimates of the proportion of people that experience progressive symptoms should be used.

- The company's method to estimate transition probabilities should be used.
- Backward transitions to healthier health states should be allowed.
- 80% of people that start receiving cerliponase alfa in health state 1 would be 'initial stabilisers'
    - 'Initial stabilisers' would stay in health state 1 for the first 6 years of cerliponase alfa treatment, after they should be assumed to transition between health states at half the rate observed for patients initiating treatment in other ML scores.
- Cerliponase alfa has no impact on vision loss.
- Health state utilities from Gissen et al. (2021) should be used.
- Electrocardiogram monitoring costs should be included.
- Neuro-disability mortality should be included in all health states.
- Psychiatric and behavioural support costs should be included.

Please could we receive the requested analyses by end of day 26 July 2024.

Kind regards,

The NICE technical team

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Highly specialised technology evaluation

# Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID6145]

# Additional analyses

**August 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6145_CerliponaseAlfa_CLN2_additional_analyses v3.0_[Redacted].docx | 3.0 | No – Redacted | 29th August 2024 |


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# List of abbreviations

| Abbreviation | Description |
|---|---|
| ACM | Appraisal committee meeting |
| CLN2 | Ceroid lipofuscinosis type 2 |
| EAG | External Assessment group |
| EAP | Expanded access programme |
| ECG | Electrocardiogram |
| FAC | Factual accuracy check |
| HST | Highly specialised technology |
| HSUV | Health state utility value |
| ICER | Incremental cost-effectiveness ratio |
| LYG | Life years gained |
| MAA | Managed access agreement |
| ML | Motor language |
| NICE | National Institute for Health and Care Excellence |
| PAS | Patient access scheme |
| QALY | Quality-adjusted life year |
| SmPC | Summary of product characteristics |
| SoC | Standard of care |


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# 1 Context

In 2019, NICE recommended cerliponase alfa for the treatment of patients with ceroid lipofuscinosis type 2 (CLN2), within the context of a managed access agreement (MAA; HST12) (1). Following the company's resubmission on 31st January 2024, and the subsequent committee meeting held on 12th June 2024, the NICE committee requested further company analyses to aid decision-making. The company considers that two of the assumptions in the committee base case are not reflective of clinical practice and therefore propose an alternative base case.

Results of the committee and the alternative company proposed base cases are presented using the discounted price for cerliponase alfa, including:

[redacted]

Results assuming either the list price or the [redacted] are presented in Appendix A.

For each analysis, incremental cost-effectiveness ratios (ICER) are presented alongside the effective HST cost-effectiveness threshold. It should be noted that it is not possible to capture the following within the cost-effectiveness estimates:

- 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 of an affected child.


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# 2 Assumptions

A summary of the assumptions for the EAG, committee, and company proposed base cases are presented in Table 3.

As noted by the committee, current NICE guidance states that, 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, a non-reference case analysis may be considered with background care costs removed (2).

CLN2 disease is associated with a high cost of care, even in the absence of active treatment. The annual cost of each type of background care is presented in Table 1.

**Table 1: Annual cost of background care**

| Type of background care | Annual cost |
|---|---|
| Health state (health and social care visits) | £5,269 to £33,539 (dependent on health state) |
| Vision loss | £4,561 |
| Psychiatric and behavioural support | £1,316 |
| Residential care | £49,359 |

Treatment with cerliponase alfa is associated with longer-term survival compared with SoC, resulting in increased background care costs that do not represent direct, intrinsic consequences of treatment.

The following background care costs were therefore excluded from the committee and company proposed base cases:

- Health state costs
- Vision loss costs
- Psychiatric and behavioural support costs
- Residential care costs.

An additional set of results is also presented for the committee base case in which background care costs are included.

The committee requested analyses for the health state distribution at model entry using data taken from current clinical practice that excludes patients where diagnosis or treatment initiation was delayed because of COVID-19. However, this analysis is not possible due to the following:


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- Data for age at CLN2 diagnosis from the clinical trial programme and from the MAA are incomplete
- It is anticipated that the effect of the COVID-19 pandemic is still a factor that may be affecting diagnosis, with some children potentially yet to be diagnosed as a direct impact of pandemic-related clinical delays (company submission Document B, Section B.2.12.2)
- Although data are available from prior to the COVID-19 pandemic, time to treatment initiation was primarily determined by when cerliponase alfa became available.
- Available data could not account for delays in CLN2 diagnosis.

There are therefore no data from the clinical trial programme and from the MAA database that are not affected by either the COVID-19 pandemic or the unavailability of cerliponase alfa at time of diagnosis for some patients. The clinician estimate of the baseline distribution in 5 years' time was therefore used in the committee base case as the best estimate of a baseline distribution unaffected by COVID-19.

The committee requested analyses considering the inclusion of starting and stopping rules for cerliponase alfa. As of July 2024, no patients have discontinued treatment with cerliponase alfa as a result of reaching the stopping criteria in the MAA. Furthermore, the clinical trial programmes for cerliponase alfa do not provide evidence for the implementation of starting and/or stopping criteria. As such, no clinical evidence exists for its implementation.

To establish starting/stopping criteria which may be used in clinical practice, the company sought insights from clinical experts and representatives of the patient advocacy group. Clinical expert opinion highlighted that given the rarity and heterogeneity of CLN2, criteria for treatment discontinuation would currently be determined on a case-by-case basis and may be dependent on numerous factors including ML score, patient-reported outcomes (PROs), and the intensity of the patient's progressive symptoms. Experts were unanimous that ML score alone is not an appropriate measure for determining treatment discontinuation. However, in clinical practice, it is expected that on average patients may discontinue treatment at an ML score of either 1 or 0, therefore a stopping rule at ML 1 was considered in the base case and ML 0 was considered as a scenario analysis.

The company has committed to consolidating and sharing additional information for consideration, once all starting and stopping criteria discussions with clinicians and patient advocacy representatives have been held.


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It is important to note that in the economic model, the ICER and threshold change in a relatively linear way in response to changes in discontinuation rates or stopping rules. Table 2 presents the results of the committee base case assuming stopping criteria at an ML score of 0 and 1 and the respective thresholds. Assuming a stopping criteria of ML 0 results in a 19% increase in the ICER, but also a 21% increase in the cost-effectiveness threshold, and so the cost-effectiveness conclusions remain unchanged. Therefore, the company does not consider stopping criteria to be a key driver of cost-effectiveness.

**Table 2: Discontinuation ICER and threshold results (with discounted price for cerliponase alfa)**

| | ICER (cost/QALY) | Threshold |
|---|---|---|
| Stopping criteria at ML 1 | [redacted] | £139,273 |
| Stopping criteria at ML 0 | [redacted] | £167,900 |
| Ratio | 1.19 | 1.21 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year.

The company base case makes two amendments to the committee base case:

- Transition probabilities are taken from Study 190-203 only:
    - As data from Study 190-201/202 encompass treatment pauses between the end of the EAP and the start of the MAA and therefore reflects transitions for more progressed patients who did not have cerliponase alfa available at the time of diagnosis.
    - Additionally, at the beginning of Study 190-201, 6 patients were enrolled in the study dose-escalation phase under the inclusion criteria of an ML score between 3 and 6 inclusive. During the escalation phase three patients experienced disease progression to ML scores of 2 and 1; these patients remained in the study as eligibility was determined according to the screening assessment ML score, and therefore these patients remained eligible for study inclusion.
- ECGs are not applied for cardiac-normal patients, in line with clinical expert advice that this would not be undertaken in clinical practice; note that an annual cardiologist appointment is applied for all patients.


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**Table 3: Base case assumptions**

| | Base case | | |
|---|---|---|---|
| | **EAG** | **Committee** | **Company proposal** |
| Baseline distribution | Aligned with HST12<br>• Health state 1: 50%<br>• Health state 2: 50% | Current clinical practice excluding patients where diagnosis or treatment initiation was delayed due to COVID-19†<br>• Health state 1: 50%<br>• Health state 2: 35%<br>• Health state 3: 13%<br>• Health state 4: 3% | |
| | | Scenario considering baseline distribution derived from clinical expert opinion‡<br>• Health state 1: 28.5%<br>• Health state 2: 28.5%<br>• Health state 3: 43.0% | - |
| Source of transition probabilities | All patients' dataset | Pooled data from Study 190-201/202 and Study 190-203 | Study 190-203 |
| Initial stabilisation | • 80% of ML 6 are initial stabilisers<br>• Stabilise for 6 years<br>• After 6 years, transition at 50% of the rate of other patients | | |
| Progressive symptoms | Assumptions aligned with the company submission (Document B, Section B.3.3.3) | | |
| Method to estimate transition probabilities | Assumptions aligned with the company submission (Document B, Section B.3.3.2) | | |
| Backward transitions to healthier health states | Permitted | | |
| Vision loss | Cerliponase alfa has no impact on vision loss | | |
| Source of HSUVs | Gissen et al. 2021 | | |


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| | Base case | | |
|---|---|---|---|
| | **EAG** | **Committee** | **Company proposal** |
| ECG monitoring costs | Included:<br>• ECG every 6 months for all patients<br>• ECG at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>• One annual cardiologist appointment for all patients | | Included:<br>• ECG included at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>• One annual cardiologist appointment for all patients |
| Neurodisability mortality | Included in all health states | | |
| Background care costs¶ | Included | Excluded<br>• Second set of results presented with background care costs included | Excluded |
| Starting and stopping criteria§ | • No starting rule<br>• Stopping rule at ML 0 | • No starting rule<br>• Stopping rule at ML 1<br><br>Scenario considering stopping rule at ML 0 | • No starting rule<br>• Stopping rule at ML 1 |

†Baseline distribution derived from clinical opinion of the distribution in 5-years' time was considered as a reasonable proxy; ‡Assuming a starting age of 3.5 years, aligned with the baseline age in the original HST12 and clinical opinion of the baseline distribution in 5-years' time; ¶Background care costs include health state costs, vision loss costs, psychiatric and behavioural support costs, and residential care costs; §In order to consider alternative starting rules in the economic model, selected starting distributions are reweighted to consider proportion in associated ML scores only.
Abbreviations: EAG, external assessment group; ECG, electrocardiogram; HSUVs, health state utility values; ML, motor language.


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# 3 Results

All results in this section use the discounted price for cerliponase alfa, considering the following discounts:

[redacted]

## 3.1 Results - committee base case

The derivation of the committee's base case (excluding background care costs) from the EAG base case at cerliponase alfa discounted price is presented in Table 4.

Additionally, the company noted and subsequently amended inconsistencies in the EAG's model; details of the amendments made are presented in Appendix B.

**Table 4: Derivation of the committee base case – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| | | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|
| 1 | EAG base case | [redacted] | [redacted] | [redacted] | £169,561† |
| 2 | 1 + vision loss correction + discontinuation correction | [redacted] | [redacted] | [redacted] | £157,941 |
| 3 | 2 + baseline distribution from clinical opinion in 5-years' time | [redacted] | [redacted] | [redacted] | £154,943 |
| 4 | 3 + transition probabilities from pooled Study 190-201/202 & 203 | [redacted] | [redacted] | [redacted] | £167,900 |
| 5 | 4 + cerliponase alfa treatment discontinuation at ML score 1 | [redacted] | [redacted] | [redacted] | £139,273 |
| 6 | 5 + background care costs removed | [redacted] | [redacted] | [redacted] | £139,273 |
| 7 | Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |

†Note, the EAG base case threshold is incorrectly reported in the following documentations: ACM slides and EAG report Table 1.
Abbreviations: ACM, Appraisal committee meeting; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year; SoC, standard of care.


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Results of the committee base case (excluding background care costs) and scenarios are presented in Table 5 and Table 6, respectively.

**Table 5: Base-case results – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care.

**Table 6: Scenario results – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Scenario | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|
| Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| Baseline distribution derived from committee clinical expert opinion | [redacted] | [redacted] | [redacted] | £100,000 |
| Treatment discontinuation at ML 0 | [redacted] | [redacted] | [redacted] | £167,900 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year; SoC, standard of care.

Results of the committee base case (including background care costs) are presented in Table 7.

**Table 7: Base-case results (including background care costs) – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care.


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## 3.2 Results – company base case proposal

The derivation of the company base case from the committee's base case is presented in Table 8, and the results of the company proposed base case considering the discounted price for cerliponase alfa are presented in Table 9.

**Table 8: Derivation of the company proposed base case – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| | | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|
| 1 | Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| 2 | 1 + transition probabilities derived from Study 190-203 | [redacted] | [redacted] | [redacted] | £213,321 |
| 3 | 2 + ECG monitoring at every infusion for cardiac abnormal patients only | [redacted] | [redacted] | [redacted] | £213,321 |
| 4 | Company base case proposal | [redacted] | [redacted] | [redacted] | £213,321 |

Abbreviations: ECG, electrocardiogram; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

**Table 9: Base-case results – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER vs baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £213,321 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.


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# 4 References

1. National Institute for Health and Care Excellence (NICE). Final evaluation document. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. 2019.

2. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (last accessed October 2023). 2022.


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# Appendix A – Results at alternative prices

## PAS price results

Results of the committee base case considering the [redacted] for cerliponase alfa are presented in Table 10, Table 11 and Table 12, with the company base case proposal presented in Table 13.

### *Committee base case*

**Table 10: Base-case results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 11: Scenario results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Scenario | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|
| Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| Baseline distribution derived from committee clinical expert opinion | [redacted] | [redacted] | [redacted] | £100,000 |
| Treatment discontinuation at ML 0 | [redacted] | [redacted] | [redacted] | £167,900 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care.


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**Table 12: Base-case results (including background care costs) – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; SoC, standard of care

### *Company base case*

**Table 13: Base-case results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £213,321 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; SoC, standard of care.

## List price results

Results of the committee base case considering the list price for cerliponase alfa are presented in Table 14, Table 15 and Table 16, with the company base case proposal presented in Table 17.


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### *Committee base case*

**Table 14: Base-case results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 15: Scenario results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Scenario | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|
| Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| Baseline distribution derived from committee clinical expert opinion | [redacted] | [redacted] | [redacted] | £100,000 |
| Treatment discontinuation at ML 0 | [redacted] | [redacted] | [redacted] | £167,900 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year; SoC, standard of care.

**Table 16: Base-case results (including background care costs) – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.


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### *Company base case*

**Table 17: Base-case results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £213,321 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.


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# Appendix B – Additional company corrections

## Vision loss approach

During the EAG factual accuracy check (FAC), the company noted that the EAG's calculation of the proportion of patients with vision loss in the model resulted in incorrect estimates of the vision loss utility multiplier. Despite this being raised by the company during the FAC, the EAG indicated that this was not an error, and highlighted that their approach was in line with HST12. Nevertheless, the company believes that this error remains, resulting in incorrect estimates for the vision loss utility multiplier.

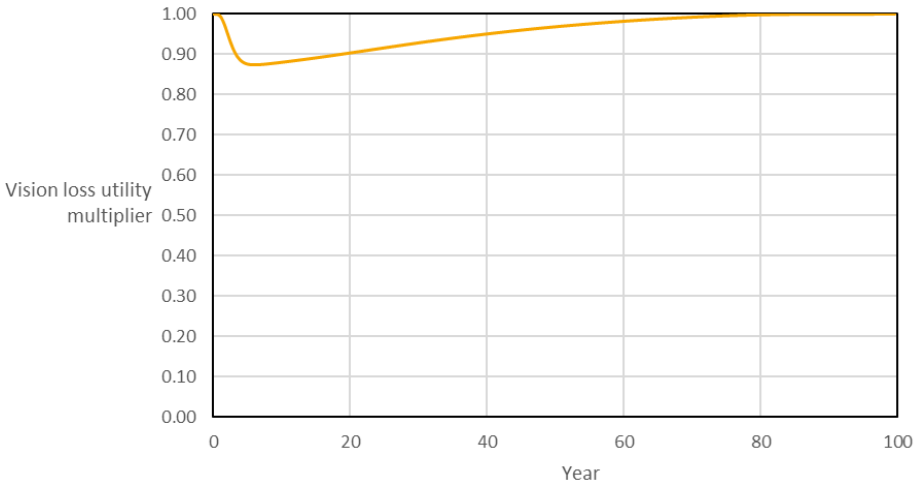
For the calculation of QALYs, the proportion of patients with vision loss is used to determine the vision loss utility multiplier, which is applied to QALY calculations of all alive patients. The approach taken by the EAG, aligned with HST12, calculates the proportion with vision loss as an absolute proportion of all modelled patients and therefore, the proportion with vision loss increases then decreases to 0% as patients enter the absorbing death state. As a result, the vision loss utility multiplier decreases initially, then increases to one as patients enter death, the absorbing state.

The proposed approach by the company is to calculate the proportion with vision loss to align with the QALY and cost calculations as follows:

- QALYs: the proportion of patients with vision loss out of all patients alive
- Costs: the total proportion of patients with vision loss

The corrected and uncorrected approaches to modelling vision loss are presented in Figure 1 and Figure 2 respectively. The corrected approach shows the multiplier reaching 0.87 once all patients experience vision loss or reach age 20 over the course of the model horizon.

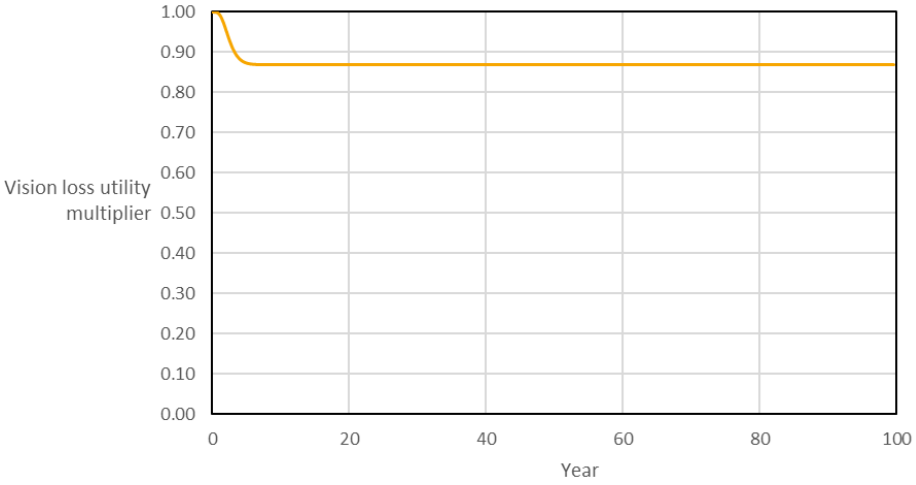
**Figure 1: Vision loss utility multiplier – HST12 approach**





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**Figure 2: Vision loss utility multiplier – Company correction**




Results presented in Section 3 adjust for the impact of correcting this assumption.

## Discontinuation transition approach

In the company's submission, once patients discontinue treatment with cerliponase alfa, they are assumed to switch to transition probabilities for standard of care (SoC). However, the EAG noted that the approach to modelling treatment discontinuation was inconsistent, remarking that once patients discontinue treatment 'some treatment effect of cerliponase alfa remains. The company has provided a correction to this assumption, in which patients receiving treatment with cerliponase alfa switch to transition probabilities for SoC, at the point of entering the health state associated with the discontinuing motor language (ML) score. Results presented in Section 3 adjust for the impact of correcting this approach.


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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Highly specialised technology evaluation

# Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID6145]

# Additional analyses addendum

**August 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6145_CerliponaseAlfa_CLN2_additional_analyses_addendum v3.0_[Redacted].docx | 3.0 | No – Redacted | 29th August 2024 |


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# List of abbreviations

| Abbreviation | Description |
|---|---|
| CLN2 | Neuronal ceroid lipofuscinosis type 2 |
| EAP | Expanded access programme |
| ECG | Electrocardiogram |
| HST | Highly specialised technology |
| ICER | Incremental cost-effectiveness ratio |
| MAA | Managed access agreement |
| ML | Motor language |
| NICE | National Institute for Health and Care Excellence |
| PAS | Patient access scheme |


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# 1 Context

In 2019, NICE recommended cerliponase alfa for the treatment of patients with neuronal ceroid lipofuscinosis type 2 (CLN2), within the context of a managed access agreement (MAA; HST12) (1). Following the Company's resubmission on 31st January 2024, and the subsequent Committee meeting held on 12th June 2024, the NICE Committee requested further Company analyses to aid decision-making alongside suggesting start and stop criteria. Whilst the Company was able to show cost-effectiveness of cerliponase alfa for CLN2 in the original submission, the Committee requested additional analyses, based on different assumptions and transition probabilities, which render the treatment not cost-effective. The Company submitted additional analyses on 26th July 2024; following further discussions with clinicians and patient groups, additional scenario analyses have been conducted exploring alternative starting and stopping rules.

Results are presented using the discounted price for cerliponase alfa, including:

[redacted]

Results assuming each of PAS price only and list price are presented in Appendix B.

It should be noted that BioMarin consider these additional scenario analyses to be highly exploratory, and do not endorse or support any starting or stopping criteria. These scenario analyses, which use hypothetical starting and stopping rules, have been presented to fulfil the request from the NICE Committee. However, there are no data or evidence from any source to support their use/adoption within UK clinical practice. Furthermore, based on feedback from the Batten Disease Family Association (BDFA) and affected families, there was unequivocal consensus that the patient community would strongly oppose the introduction of any starting or stopping criteria.

However, BioMarin believes there are opportunities to improve the starting ML scores of the patient population without any requirement for starting criteria, which would be devastating for the patient community. As part of the original evaluation of cerliponase alfa (HST12), approaches that would have enabled broad access to diagnostic services, such as the Blueprint Genetics program – a comprehensive diagnostic panel of more than 500 genetic epilepsy-related diseases in children aged 24–48 months – was planned in collaboration with


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NHS England (2). Currently, only cases undergoing screening for clinical trials are submitted to the program. Nevertheless, BioMarin remain committed to continuing and expanding the development of an early diagnosis programme with NHS England. BioMarin anticipates that if newborn screening and the earlier diagnosis programme were implemented in England, then the estimated motor-language (ML) score at diagnosis would be equal to or greater than 5.


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# 2 Assumptions

Scenario analyses have been conducted for both the Committee base case and the Company-proposed base case. An additional set of results is presented for the Committee base case in which background care costs are included. The Company-proposed base case is consistent with the Committee base case with the exception of the following:

- Transition probabilities are derived from Study 190-203
- Electrocardiogram (ECG) costs are included at every infusion for patients with cardiac history and one annual cardiologist appointment is included for all patients.

A summary of the Committee and Company proposed base cases is presented in Appendix A, Table 4. Results assuming each of PAS price only and list price are presented in Appendix B.

Considered scenario analyses include:

- Starting populations of:
    - ML score 5 and 6
    - ML score 6 only
    - ML score 6 and a starting age of 0 (reflecting newborn screening)
- Stopping rules at:
    - ML score 3
    - ML score 2
    - ML score 0
    - No stopping rule.


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Clinical experts were consulted to elicit potential alternative starting and stopping criteria and noted that given the rarity and heterogeneity of CLN2, the following factors may be considered as potential triggers to discuss the appropriateness of maintaining or interrupting therapy with the families of patients with CLN2:

- ML score
- Patient-reported outcomes (PRO)
- The patient's progressive symptoms, including seizures, dystonia, pain, spasticity, and myoclonus.

Clinicians did not believe that the decision to discontinue could be made solely on ML score, and noted that in some cases PRO instruments may be more suitable than ML score to inform discussions with families.

It is not possible to include all of these factors in the economic model, and it may be expected that patients would discontinue treatment at different ML scores, rather than all patients discontinuing treatment at a specified ML score (as considered in the scenario analyses). However, for all scenario analyses considering alternative stopping rules, the percentage change in the incremental cost-effectiveness ratio (ICER) was found to be consistent with the percentage change in the willingness-to-pay threshold (i.e. the scenario did not change the assessment of cost-effectiveness). The choice of stopping rule is therefore not expected to be a determinant of cost-effectiveness.


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# 3 Results

All results in this section use the discounted price for cerliponase alfa, considering the following discounts:

[redacted]

Results of scenario analysis derived from the company proposed base case, the committee base case (excluding background care costs) and the committee base case (including background care costs) are presented in Table 1,Table 2 and Table 3, respectively.

**Table 1: Scenario analyses – Company proposed base case (cerliponase alfa discounted price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £213,321 | - |
| Starting rule | ML 5 or 6 | [redacted] | -2.1% | £239,297 | 12.2% |
| | ML 6 | [redacted] | -6.1% | £300,000 | 40.6% |
| | ML 6 and age 0 | [redacted] | -7.5% | £300,000 | 40.6% |
| Stopping rule | ML 3 | [redacted] | -13.3% | £178,161 | -16.5% |
| | ML 2 | [redacted] | -10.2% | £191,605 | -10.2% |
| | ML 0 | [redacted] | 13.8% | £242,865 | 13.8% |
| | No stopping rule | [redacted] | 18.2% | £249,664 | 17.0% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language.


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**Table 2: Scenario analyses – Committee base case (excluding background care costs; cerliponase alfa discounted price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £139,273 | - |
| Starting rule | ML 5 or 6 | [redacted] | -2.7% | £156,678 | 12.5% |
| | ML 6 | [redacted] | -10.2% | £222,716 | 59.9% |
| | ML 6 and age 0 | [redacted] | -11.6% | £223,506 | 60.5% |
| Stopping rule | ML 3 | [redacted] | -20.1% | £112,413 | -19.3% |
| | ML 2 | [redacted] | -13.4% | £121,674 | -12.6% |
| | ML 0 | [redacted] | 19.0% | £167,900 | 20.6% |
| | No stopping rule | [redacted] | 25.1% | £176,219 | 26.5% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language.

**Table 3: Scenario analyses – Committee base case (including background care costs; cerliponase alfa discounted price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £139,273 | - |
| Starting rule | ML 5 or 6 | [redacted] | -2.9% | £156,678 | 12.5% |
| | ML 6 | [redacted] | -10.9% | £222,716 | 59.9% |
| | ML 6 and age 0 | [redacted] | -12.4% | £223,506 | 60.5% |
| Stopping rule | ML 3 | [redacted] | -24.8% | £112,413 | -19.3% |
| | ML 2 | [redacted] | -16.6% | £121,674 | -12.6% |
| | ML 0 | [redacted] | 22.1% | £167,900 | 20.6% |
| | No stopping rule | [redacted] | 28.2% | £176,219 | 26.5% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language.


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# 4 References

1. National Institute for Health and Care Excellence (NICE). Final evaluation document. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. 2019.

2. Blueprint Genetics. Diagnostic Program. Available at: https://blueprintgenetics.com/beyondpaediatricepilepsy/ (last accessed January 2024). 2017.


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# Appendix A – Base-case assumptions

**Table 4: Base case assumptions**

| | Base case | |
|---|---|---|
| | **Committee** | **Company proposal** |
| Baseline distribution | Current clinical practice excluding patients where diagnosis or treatment initiation was delayed due to COVID-19†<br>• Health state 1: 50%<br>• Health state 2: 35%<br>• Health state 3: 13%<br>• Health state 4: 3% | |
| | Scenario considering baseline distribution derived from clinical expert opinion‡<br>• Health state 1: 28.5%<br>• Health state 2: 28.5%<br>• Health state 3: 43.0% | – |
| Source of transition probabilities | Pooled data from Study 190-201/202 and Study 190-203 | Study 190-203 |
| Initial stabilisation | • 80% of ML 6 are initial stabilisers<br>• Stabilise for 6 years<br>• After 6 years, transition at 50% of the rate of other patients | |
| Progressive symptoms | Assumptions aligned with the Company submission (Document B, Section B.3.3.3) | |
| Method to estimate transition probabilities | Assumptions aligned with the Company submission (Document B, Section B.3.3.2) | |
| Backward transitions to healthier health states | Permitted | |
| Vision loss | Cerliponase alfa has no impact on vision loss | |
| Source of HSUVs | Gissen et al, 2021 | |
| ECG monitoring costs | Included:<br>• ECG every 6 months for all patients<br>• ECG at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>• One annual cardiologist appointment for all patients | Included:<br>• ECG included at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>• One annual cardiologist appointment for all patients |
| Neurodisability mortality | Included in all health states | |


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| | Base case | |
|---|---|---|
| | **Committee** | **Company proposal** |
| Background care costs¶ | Excluded<br>• Second set of results presented with background care costs included | Excluded |
| Starting and stopping criteria§ | • No starting rule<br>• Stopping rule at ML 1 | |

†Baseline distribution derived from clinical opinion of the distribution in 5-years' time was considered as a reasonable proxy; ‡Assuming a starting age of 3.5 years, aligned with the baseline age in the original HST12 and clinical opinion of the baseline distribution in 5-years' time; ¶Background care costs include health state costs, vision loss costs, psychiatric and behavioural support costs, and residential care costs; §In order to consider alternative starting rules in the economic model, selected starting distributions are reweighted to consider proportion in associated ML scores only.
Abbreviations: EAG, external assessment group; ECG, electrocardiogram; HSUV, health state utility value; ML, motor language.


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# Appendix B – Results at alternative prices

## PAS price results

Results considering the [redacted] for cerliponase alfa are presented in Table 5, Table 6 and Table 7 for the company proposed base case, the committee base case (excluding background care costs) and the committee base case (including background care costs), respectively.

**Table 5: Scenario analyses – Company proposed base case (cerliponase alfa PAS price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £213,321 | - |
| Starting rule | ML 5 or 6 | [redacted] | -2.3% | £239,297 | 12.2% |
| | ML 6 | [redacted] | -6.6% | £300,000 | 40.6% |
| | ML 6 and age 0 | [redacted] | -9.5% | £300,000 | 40.6% |
| Stopping rule | ML 3 | [redacted] | -12.7% | £178,161 | -16.5% |
| | ML 2 | [redacted] | -9.7% | £191,605 | -10.2% |
| | ML 0 | [redacted] | 13.2% | £242,865 | 13.8% |
| | No stopping rule | [redacted] | 17.4% | £249,664 | 17.0% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; PAS, patient access scheme.

**Table 6: Scenario analyses – Committee base case (excluding background care costs; cerliponase alfa PAS price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £139,273 | - |
| Starting rule | ML 5 or 6 | [redacted] | -2.9% | £156,678 | 12.5% |
| | ML 6 | [redacted] | -10.9% | £222,716 | 59.9% |
| | ML 6 and age 0 | [redacted] | -14.0% | £223,506 | 60.5% |
| Stopping rule | ML 3 | [redacted] | -19.2% | £112,413 | -19.3% |
| | ML 2 | [redacted] | -12.6% | £121,674 | -12.6% |


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| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| | ML 0 | [redacted] | 18.1% | £167,900 | 20.6% |
| | No stopping rule | [redacted] | 23.9% | £176,219 | 26.5% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; PAS, patient access scheme.

**Table 7: Scenario analyses – Committee base case (including background care costs; cerliponase alfa PAS price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £139,273 | - |
| Starting rule | ML 5 or 6 | [redacted] | -3.0% | £156,678 | 12.5% |
| | ML 6 | [redacted] | -11.4% | £222,716 | 59.9% |
| | ML 6 and age 0 | [redacted] | -14.4% | £223,506 | 60.5% |
| Stopping rule | ML 3 | [redacted] | -22.4% | £112,413 | -19.3% |
| | ML 2 | [redacted] | -14.9% | £121,674 | -12.6% |
| | ML 0 | [redacted] | 20.2% | £167,900 | 20.6% |
| | No stopping rule | [redacted] | 26.1% | £176,219 | 26.5% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; PAS, patient access scheme.

## List price results

Results considering the list price for cerliponase alfa are presented in Table 8, Table 9 and Table 10 for the company proposed base case, the committee base case (excluding background care costs) and the committee base case (including background care costs), respectively.

**Table 8: Scenario analyses – Company proposed base case (cerliponase alfa list price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £213,321 | - |
| Starting rule | ML 5 or 6 | [redacted] | -2.3% | £239,297 | 12.2% |
| | ML 6 | [redacted] | -6.6% | £300,000 | 40.6% |
| | ML 6 and age 0 | [redacted] | -9.5% | £300,000 | 40.6% |


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| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Stopping rule | ML 3 | [redacted] | -12.7% | £178,161 | -16.5% |
| | ML 2 | [redacted] | -9.7% | £191,605 | -10.2% |
| | ML 0 | [redacted] | 13.2% | £242,865 | 13.8% |
| | No stopping rule | [redacted] | 17.4% | £249,664 | 17.0% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language.

**Table 9: Scenario analyses – Committee base case (excluding background care costs; cerliponase alfa list price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £139,273 | - |
| Starting rule | ML 5 or 6 | [redacted] | -2.9% | £156,678 | 12.5% |
| | ML 6 | [redacted] | -10.9% | £222,716 | 59.9% |
| | ML 6 and age 0 | [redacted] | -14.0% | £223,506 | 60.5% |
| Stopping rule | ML 3 | [redacted] | -19.2% | £112,413 | -19.3% |
| | ML 2 | [redacted] | -12.6% | £121,674 | -12.6% |
| | ML 0 | [redacted] | 18.1% | £167,900 | 20.6% |
| | No stopping rule | [redacted] | 23.9% | £176,219 | 26.5% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language.

**Table 10: Scenario analyses – Committee base case (including background care costs; cerliponase alfa list price)**

| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| Base case | | [redacted] | - | £139,273 | - |
| Starting rule | ML 5 or 6 | [redacted] | -3.0% | £156,678 | 12.5% |
| | ML 6 | [redacted] | -11.2% | £222,716 | 59.9% |
| | ML 6 and age 0 | [redacted] | -14.3% | £223,506 | 60.5% |
| Stopping rule | ML 3 | [redacted] | -21.3% | £112,413 | -19.3% |
| | ML 2 | [redacted] | -14.1% | £121,674 | -12.6% |
| | ML 0 | [redacted] | 19.4% | £167,900 | 20.6% |


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| Scenario | | ICER | % change from base-case ICER | Threshold | % change from base-case threshold |
|---|---|---|---|---|---|
| | No stopping rule | [redacted] | 25.3% | £176,219 | 26.5% |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language.


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# CONFIDENTIAL UNTIL PUBLISHED
# External Assessment Group Review of the Additional Evidence Submitted by the Company after ACM1

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]


| | |
|---|---|
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## 1. Introduction

The External Assessment Group (EAG) was requested by NICE to review and critique the additional evidence submitted by the company in response to NICE's request for further evidence following the first appraisal committee meeting (ACM1) on 12 June 2024. The key elements of company's response were:

1. An updated version of the economic model submitted by the EAG alongside the evidence assessment report (EAR) with:
    1.1. Functionality to run additional analyses requested by the committee;
    1.2. Changes to the vision loss modelling approach and the assumptions on maintenance of cerliponase alfa treatment effect upon treatment discontinuation.
2. Deterministic cost-effectiveness results for:
    2.1. An analysis incorporating the company's interpretation of the committee's preferred assumptions;
    2.2. The company's proposed base case analysis including some of the committee's preferred assumptions at ACM1;
    2.3. Scenario analyses exploring alternative assumptions on the i) patient baseline distribution and ii) cerliponase alfa stopping rule performed over the company's interpretation of the committee's preferred assumptions (i.e., the analysis mentioned in 2.1.).
3. An addendum containing deterministic cost-effectiveness results for scenario analyses exploring different starting populations and cerliponase alfa stopping rules (performed over i) the company's interpretation of the committee's preferred assumptions (i.e., the analysis in 2.1.) and ii) the company's proposed base case).

Due to the limited time available, the additional work undertaken by the EAG does not constitute a formal critique of the company's response and, hence, does not accord with the procedures and templates applied to the original submission. The EAG checked, however, the implementation of the proposed model changes and successfully replicated the main results presented by the company.

The remainder of this report includes four sections and one appendix. Section 2 reports the committee's preferred assumptions and lists the additional analyses requested after ACM1. Section 3 presents an overview of the economic model updates and additional analyses presented by the company along with a critique of this evidence by the EAG. Section 4 presents the results of further cost-effectiveness analyses carried out by the EAG. Section 5 presents the conclusions of this report. Similarly to the EAR, cost-effectiveness results presented in the main body of this report (Sections 3, 4 and 5) incorporate the company's list price for cerliponase alfa, while results incorporating a patient access scheme (PAS) price corresponding to a [redacted] are shown in an

appendix (Appendix 1). [redacted]

## 2. Overview of the appraisal committee's preferred assumptions and further analyses requested

At ACM1 the committee's preferred assumptions to be considered in the company's additional analysis should be as follows:

- The company's estimates of the proportion of people that experience progressive symptoms should be used.
- The company's method to estimate transition probabilities should be used.
- Using as evidence source to inform the transition probabilities the 'all patient' pooled dataset in the EAG's base-case (although the committee acknowledge the impact of the COVID-19 pandemic on the data collected in the context of the managed access agreement (MAA)).
- Backward transitions to healthier health states should be allowed.
- 80% of people that start receiving cerliponase alfa in health state (HS)1 would be 'initial stabilisers':
    - 'Initial stabilisers' would stay in HS1 for the first 6 years of cerliponase alfa treatment, after they should be assumed to transition between health states at half the rate observed for patients initiating treatment in other ML scores.
- Cerliponase alfa has no impact on vision loss.
- Health state utilities from Gissen et al. (2021)[1] should be used.
- Electrocardiogram (ECG) monitoring costs should be included.
- Neuro-disability mortality should be included in all health states.
- Psychiatric and behavioural support costs should be included.

The committee noted a number of areas of unresolved uncertainty and requested further analyses to address these, namely:

1. <u>Baseline distribution across health states</u>
   The committee considered the baseline distribution applied in the EAG base case was too optimistic (50% HS1 and 50% HS2) but the EAG's clinical expert current clinical practice scenario was too conservative (15% HS1, 45% HS2, 30% HS3 and 10% HS4). The committee further stated that the baseline distribution suggested by one of the clinical experts at ACM1 (28.5% HS1, 28.5% HS2 and 42% HS3[a]) was plausible and could be used in a scenario analysis. The committee requested further analysis using data taken from current clinical practice that

[a] We note that this distribution does not add to 100%. It was assumed in the company and EAG analyses applying this distribution (presented in subsequent sections) that 43% of patients would be in HS3 at model start, so as to ensure that the baseline distribution of patients adds to 100%.

excludes patients where diagnosis or treatment initiation was delayed because of COVID-19 to inform the baseline distribution in the model.

2. Evidence source to inform the transition probabilities:
   Analysis using pooled data across studies (190-203 and 190-201/202) and excluding the MAA data to explore the potential impact of the COVID-19 pandemic on the transition probabilities.
3. Starting and stopping rules:
   Analyses that consider the inclusion of starting and stopping rules into the model. These starting and stopping rules should be used to identify subgroups of individuals for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost-effective.
4. Non-reference-case-analysis
   Analysis with background care costs removed.

## 3. Company's economic model updates and additional analyses

### 3.1. Economic model updates

The company updated the version of their economic model submitted by the EAG alongside the EAR by adding functionality to explore the impact of:

i) Alternative baseline patient distributions according to health state (referred to as "starting populations" by the company in their addendum);
ii) Informing transition probabilities with pooled data from Study 190-201/202 and Study 190-203 (excluding MAA).
iii) Excluding background care costs (the company only included the costs associated with the drug acquisition, administration, monitoring and managing adverse treatment effects of cerliponase alfa).

Table 1 shows the 2-week transition probabilities by treatment group as informed by from Study 190-201/202 and Study 190-203 (excluding MAA), alongside the committee's ('all patients') and the company's (Study 190-203) preferred sources of evidence of evidence for these parameters.

**Table 1 Transition probabilities in the model by evidence source**

| ML score | Health state | All patients | | Study 190-201/202 & 190-203 (excluding MAA) | | Study 190-203 | |
|---|---|---|---|---|---|---|---|
| | | Cerliponase alfa | SoC | Cerliponase alfa | SoC | Cerliponase alfa | SoC |
| 0 to 1 | 7 to 6 | 6.1% | | 6.1% | | 6.1% | |
| 1 to 0 | 6 to 7 | 1.5% | 7.6% | 1.5% | 8.1% | 1.5% | 7.1% |
| 1 to 2 | 6 to 5 | 2.7% | | 2.7% | | 2.7% | |
| 2 to 1 | 5 to 6 | 2.1% | 9.2% | 2.4% | 10.4% | 2.1% | 10.1% |
| 2 to 3 | 5 to 4 | 1.3% | | 1.6% | | 1.1% | |
| 3 to 2 | 4 to 5 | 3.7% | 11.1% | 4.3% | 11.3% | 6.4% | 11.6% |
| 3 to 4 | 4 to 3 | 2.5% | | 3.1% | | 7.2% | |
| 4 to 3 | 3 to 4 | 5.8% | 7.6% | 5.0% | 9.8% | 6.6% | 12.1% |
| 4 to 5 | 3 to 2 | 0.6% | | 0.7% | | 0.9% | |
| 5 to 4 | 2 to 3 | 6.7% | 7.3% | 6.8% | 6.6% | 5.4% | 5.6% |
| 5 to 6 | 2 to 1 | 2.6% | | 2.3% | | 5.8% | |
| 6 to 5 | 1 to 2 | 0.7% | 6.3% | 0.5% | 5.0% | 0.5% | 4.6% |

**Abbreviations**: ML, motor language; SoC, standard of care.

As mentioned in Section 2, the committee requested an analysis using pooled data across studies (190-203 and 190-201/202) and excluding the MAA data to explore the potential impact of the COVID-19 pandemic on the transition probabilities. The company included these data but highlights

in their response that there are no data from the clinical trial programme and from the MAA database that are not affected by either the COVID-19 pandemic or the unavailability of cerliponase alfa at time of diagnosis for some patients.

The company also implemented changes to the EAG's vision loss modelling approach the EAG whereby cerliponase alfa was assumed to have no impact on vision loss compared to the standard of care (SoC), in line with the original highly specialised technology appraisal 12 (HST 12). The company had stated at the factual accuracy check that the EAG's calculation of the proportion of patients with vision loss in the model resulted in incorrect estimates of the vision loss utility multiplier. The EAG reiterates that this was a modelling choice rather than an error and that it was taken in line in with how vision loss had been implemented in the original HST12 model. Notwithstanding this, the EAG has considered the company's correction and the rationale for it (as detailed in Appendix B of the company's response) and concluded that the correction yields more consistent values for the vision utility multiplier. Therefore, the EAG accepts the company's correction to the vision loss modelling approach.

Finally, the company corrected the assumption that once patients discontinue treatment with cerliponase alfa, they are assumed to switch to transition probabilities for SoC, as the EAG noted in the EAR that this implies treatment effect of cerliponase alfa remains while patients do not move to the subsequent health state after treatment discontinuation. The original assumption also allowed for patients to undergo retreatment with cerliponase alfa. The company has provided a correction to this assumption, in which patients receiving treatment with cerliponase alfa switch to transition probabilities for SoC, at the point of entering the health state associated with the discontinuing motor language (ML) score. The EAG notes that this implies an immediate cessation of treatment effect upon cerliponase alfa discontinuation and that according to clinical advice received by the EAG treatment effect may persist for some time after discontinuation. Given the model structure, the EAG considers that this simplification is acceptable. However, the company only applied this correction to the transition probability of 'initial stabilisers' in the model. The company does not justify this. Therefore, the EAG implemented a further correction to the model, whereby the correction is applied to both 'initial stabilisers' and 'non-stabilisers' (see Section 4).

## 3.2. Company's additional analyses

### 3.2.1. Company and committee's preferred assumptions

The company presents in their response two alternative main analyses reflecting the: i) company's interpretation of the committee's preferred assumptions and ii) the company's proposed base case assumptions. The EAG notes that the company's interpretation of the committee's preferred

assumptions does not match the committee's stated preferences (see Section 2). Therefore, in this section the EAG does not report the analyses for what the company refers to in their response as the "committee's base case". Table 2 contrasts the preferred assumptions stated by the committee, the company's interpretation of the committee's preferred assumptions and the company's proposed base case assumptions. Table 3 shows the deterministic results of the company's proposed base case analysis.

**Table 2 Preferred assumptions by the committee and the company**

| | **Committee stated preferences** | **Company's interpretation of the committee's preference** | **Company's proposed base case** |
|---|---|---|---|
| Baseline distribution:<br>▪ HS1<br>▪ HS2<br>▪ HS3<br>▪ HS4 | Preference not stated | Population in clinical practice in 5 years time*<br>50%<br>35%<br>12.5%<br>2.5% | |
| Source of transition probabilities | Pooled 'all patients' dataset (matched to Study 190-901) | Pooled data from Study 190-201/202 and Study 190-203, excluding MAA data (matched to Study 190-901) | Study 190-203 (matched to Study 190-901) |
| Initial stabilisation | 80% of ML 6 are initial stabilisers<br>Stabilise for 6 years<br>After 6 years, transition at 50% of the rate of other patients | | |
| Progressive symptoms | Assumptions aligned with the Company submission (Document B, Section B.3.3.3) | | |
| Method to estimate transition probabilities | Assumptions aligned with the Company submission (Document B, Section B.3.3.2) | | |
| Backward transitions to healthier health states | Permitted | | |
| Vision loss | Cerliponase alfa has no impact on vision loss | | |
| Source of HSUVs | Gissen et al. (2021)[1] | | |
| Neuro-disability mortality | Included in all health states | | |
| Starting and stopping criteria | No preference stated | No starting rule<br>Stopping rule at ML 1 | |
| ECG monitoring costs included | ECG every 6 months for all patients<br>ECG at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>One annual cardiologist appointment for all patients | | ECG at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>One annual cardiologist appointment for all patients |
| Background care costs¶ | Include | Exclude | |

*According to clinical advice received by the EAG.

**Abbreviations:** EAG, external assessment group; ECG, electrocardiogram; HS, health state; HSUV, health state utility value; ML, motor language. ¶Background care costs include health state costs, vision loss costs, psychiatric and behavioural support costs, and residential care costs.

The company considered their base assumptions consistent with the committee's with the exception of the following:

- Transition probabilities are derived from Study 190-203;
- Electrocardiogram (ECG) costs are included at every infusion for patients with cardiac history and one annual cardiologist appointment is included for all patients.

The company justified the use of Study 190-203 to inform transition probabilities due to the following issues affecting Study 190-201/202:

- Study 190-201/202 encompass treatment pauses between the end of the early access programme and the start of the MAA and therefore reflects transitions for more progressed patients who did not have cerliponase alfa available at the time of diagnosis.
- Inclusion of 6 patients enrolled in the study dose-escalation phase under the inclusion criteria of an ML score between 3 and 6 inclusive, three of which experienced disease progression to ML scores of 2 and 1.

The company also stated that it was not appropriate to include ECG monitoring every 6 months, while on treatment with cerliponase alfa, and that they received clinical advice suggesting that patients considered “cardiac-normal” would not be monitored (beyond an annual cardiologist appointment).

**Table 3 Company's proposed base-case results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incr. costs (£) | Incr. LYG | Incr. QALYs | ICER (£/QALY) | CE threshold* £/QALY | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | All utilities | Excluding carer and sibling utilities |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £213,321 | NR |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

**Abbreviations:** ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not reported; QALYs, quality-adjusted life years; SoC, standard of care.

***Points for critique***

The EAG considers that the company has misinterpreted the committee's position regarding their preferred:

i. baseline patient distribution;
ii. evidence source for the transition probabilities;
iii. treatment discontinuation rules;
iv. approach to background costs.

The committee did not state its preferred assumptions for i. and iii., and the exclusion of background costs was only requested as a non-reference-case analysis. Regarding the evidence source for the transition probabilities, the committee preferred the 'all patients' pooled data. The pooled data from Study 190-201/202 and Study 190-203 (excluding MAA data) was only requested to explore the impact of the COVID-19 pandemic on the MAA. Thus, the EAG considers that, overall, the analyses provided by the company do not reflect the committee's preferred assumptions and presents further analyses in Section 4.

The EAG disagrees with the company's base case selection of evidence source for transition probabilities and the exclusion of regular ECG monitoring in the model, because these directly contradict the committee's preferences. Despite the arguments presented by the company, the EAG reiterates that the use of Study 190-203 as preferred source of evidence for the transition probabilities introduces considerable uncertainty and potential bias favouring cerliponase alfa into the cost-effectiveness analysis. As highlighted in the EAR, the EAG considers that the pooled 'all patients' data (n=35) is the most appropriate source of evidence to inform the transition probabilities in health states 1-7, because this source reflects the majority of existing evidence for these parameters due to sample size and overall length of follow-up. The data provided by Study 190-203 is affected by high uncertainty due to small numbers of patients (n=14) and the limited duration of follow-up in Study 190-203 with only some patients being followed up to 6 years. Furthermore, the Study 190-203 population may reflect a patient population younger and at an earlier point of disease progression than patients in clinical practice (see Section 4.2.4, EAR).

The EAG acknowledges the clinical advice received by the company that assuming ECG monitoring every 6 months as recommended by the cerliponase alfa summary of product characteristics may not be implemented in clinical practice. However, the EAG also notes that the assumption that the proportion of patients who have cardiac abnormalities (and therefore require an ECG at every infusion) remains constant beyond 3.5 years (27% in the EAG base-case analysis; see EAR) may underestimate the costs associated with monitoring these patients. Thus, the proportion of patients

requiring ECG monitoring is uncertain and the EAG does not consider it unduly conservative to maintain the assumption of ECG monitoring every 6 months for all patients, as the proportion of patients with cardiac abnormalities over time may be underestimated.

### 3.2.2. Company's exploratory analyses - starting and stopping rules

The committee also requested analyses that consider the inclusion of starting and stopping rules into the model to identify subgroups of individuals for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost-effective.

The company sought clinical and patient advocacy group advice to inform their analyses exploring alternative starting/stopping criteria which may be used in clinical practice. According to expert advice to the company, given the rarity and heterogeneity of CLN2, criteria for treatment discontinuation would currently be determined on a case-by-case basis and may be dependent on numerous factors including ML score, patient-reported outcomes and the intensity of the patient's progressive symptoms. Thus, it would not be appropriate to determine treatment discontinuation based on ML score alone. The company anticipates that in clinical practice patients may discontinue treatment at an ML score of either 1 or 0.

The company highlighted that their analyses on starting and stopping criteria are highly exploratory, and that there are no data or evidence from any source to support their use/adoption within UK clinical practice. The company stated that as of July 2024, no patients have discontinued treatment with cerliponase alfa as a result of reaching the stopping criteria in the MAA. Furthermore, the clinical trial programmes for cerliponase alfa do not provide evidence for the implementation of starting and/or stopping criteria. The company also noted that feedback from the Batten Disease Family Association and affected families suggested that the patient community would strongly oppose the introduction of any starting or stopping criteria. The company do not endorse or support any starting or stopping criteria.

In the addendum to the company's response, the company presents scenario analyses performed over their base case analysis (and the company's interpretation of the committee's preference) to explore alternative starting and stopping rule criteria for cerliponase alfa. In these analyses, the company explored four alternative stopping rules at: ML score 3, ML score 2, ML score 0, and no discontinuation. The company also explored three alternative baseline patient distributions representing alternative starting populations of individuals:

- Distributed across ML score 5 and 6 – in these analyses, the selected baseline distribution (i.e., the clinician estimate of the baseline distribution in 5 years' time according to clinical

advice to the EAG, see Table 2) are reweighted to consider proportion in associated ML scores only, which results in the 59% and 41% of patients in HS1 and HS2 respectively).

- ML score 6 only;
- ML score 6 and a starting age of 0, which the company considered a reflection of patients identified through newborn screening.

However, these were not performed at the cerliponase alfa list price or simple PAS price of [redacted]. The EAG did not attempt to replicate these analyses at alternative prices, and, thus, the results are not presented here.

***Points for critique***

Similarly to the company's analyses in Section 3.2.1, the EAG considers that these exploratory analyses do not reflect the committee's preferred assumptions and, therefore, are not very informative. Furthermore, the EAG considers that the analyses presented by the company may not fully comply with the request of the committee as these only explore a small subset of the alternative populations defined by different starting and stopping criteria. The EAG presents further analyses in Section 4.3.

# 4. EAG's analyses

## 4.1. Company corrected base-case analysis

As mentioned in Section 3.1, the EAG corrected the company's version of the economic model by extending the company's correction to the treatment effect upon cerliponase alfa discontinuation (see Section 3.1) to apply to both 'initial stabilisers' and non-stabilisers'. Table 4 shows the deterministic results of correcting the company's proposed base-case.

**Table 4 Company's corrected base-case results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs | Total QALYs | Incr. costs | Incr. QALYs | ICER (/QALY) | CE threshold* /QALY | |
|---|---|---|---|---|---|---|---|
| | | | | | | **All utilities** | **Excluding carer and sibling utilities** |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £200,704 | £194,964 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |

**Abbreviations:** ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

Compared to the company's proposed base-case, this analyses suggests lower incremental costs and QALYs for cerliponase alfa vs. SoC, and results in a lower incremental cost-effectiveness ratio (ICER) but it also decreases the implied cost-effectiveness threshold. The EAG notes that the company does not report the implied cost-effectiveness threshold when only patients' utilities are considered in the estimation of the undiscounted incremental QALYs.

### 4.2. EAG's base case and scenario analyses

The EAG developed a revised base case analyses by aligning the assumptions with those preferred by the committee at ACM1. For assumption for which the committee did not state a preference, the EAG retained the assumptions on the original EAG base case and then explored alternative assumptions in scenario analyses. The only exception to this was the assumption on baseline distribution. The differences in the preferred assumptions between the EAG and company's base case analyses are listed in Table 5.

**Table 5 Differences between the EAG and company's base case analyses**

| | **EAG revised base-case** | **Company's corrected base case** |
|---|---|---|
| Baseline distribution: | | |
| ▪ HS1 | 28.5% | 50% |
| ▪ HS2 | 28.5% | 35% |
| ▪ HS3 | 43% | 12.5% |
| ▪ HS4 | 0% | 2.5% |
| Source of transition probabilities | Pooled 'all patients' dataset matched to Study 190-901 | Study 190-203 matched to Study 190-901 |
| Starting and stopping criteria§ | No starting rule<br>Stopping rule at ML 0 (HS7) | No starting rule<br>Stopping rule at ML 1 (HS6) |
| ECG monitoring costs included | ECG every 6 months for all patients<br>ECG at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>One annual cardiologist appointment for all patients | ECG at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>One annual cardiologist appointment for all patients |
| Background care costs¶ | Included | Excluded |

**Abbreviations:** EAG, external assessment group; ECG, electrocardiogram; HS, health state; HSUV, health state utility value; ML, motor language. ¶Background care costs include health state costs, vision loss costs, psychiatric and behavioural support costs, and residential care costs

As mentioned in Section 2, the committee considered the baseline distribution applied in the original EAG base case too optimistic and the EAG's clinical expert current clinical practice scenario was too conservative. The committee considered that the baseline distribution suggested by one of the clinical experts at ACM1 was plausible and appropriate for scenario analysis. In the absence of a committee preferred assumption for the baseline distribution, the EAG uses the baseline distributions suggested

by the clinical expert at ACM1 in the revised base case analysis, and explores alternative distributions in scenario analyses.

The EAG conducted further scenario analyses over the revised base case to address areas of remaining uncertainty identified by the committee. Scenario 1 applies the clinician estimate of the baseline distribution in 5 years' time according to clinical advice to the EAG, which was considered by the company the best estimate of a baseline distribution unaffected by COVID-19 (in the absence of suitable empirical data to inform these parameters). Scenario 2 applies the EAG original base case assumption for baseline distribution. Scenario 3 utilises the pooled data from Study 190-201/202 and Study 190-203 excluding MAA, matched to Study 190-901, as the evidence source for transition probabilities. Scenarios 4 and 5 apply alternative stopping rules for cerliponase alfa treatment. Scenario 6 represents the non-reference analysis excluding background care cost, as requested by the committee.

Deterministic results of the EAG's revised base case and scenario analyses are reported alongside the company's corrected base-case in Table 6.

The EAG base case analysis suggests an ICER of [redacted] per additional QALY and a cost-effectiveness threshold of £100,000 (regardless of whether all utilities or only patient utilities are considered). The differences between the EAG and the company's base case analysis are driven by the baseline patient distribution, the source of evidence to inform the transition probabilities and the treatment discontinuation. Excluding background care costs has a modest impact on the ICER for cerliponase alfa vs. SoC.

In regard to the treatment discontinuation rule, the EAG notes that under the corrections applied by the company, all analyses now assume that no treatment effect of cerliponase alfa on the transition probabilities remains once treatment is stopped. This is more conservative in terms of the impact of cerliponase alfa on disease progression than the original company assumption. However, it also means that backward transitions from the health state at which patients discontinue to the previous health state no longer occur and, therefore, retreatment with cerliponase alfa is no longer considered in the model. Therefore, the EAG concerns about retreatment being inconsistent with current clinical practice are assuaged.

**Table 6 Cost-effectiveness results of the EAG's base case and scenario analyses (cerliponase alfa list price)**

| Preferred assumption | Total Costs | Total QALYs | Incr. cost | Incr. QALYs | ICER £/QALY | CE threshold* £/QALY | |
|---|---|---|---|---|---|---|---|
| | | | | | | All utilities | Excluding carer and sibling utilities |
| **Company's corrected base case** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £200,704 | £194,964 |
| **EAG revised base-case** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £100,000 | £100,000 |
| **Scenario 1. EAG base-case + Baseline characteristics as per clinical opinion of current practice in 5-year time (company's corrected base-case)** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £139,528 | £137,428 |
| **Scenario 2. EAG base-case + Baseline characteristics as per EAG's original base-case (HS1 50%, HS2 50%)** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £142,584 | £140,405 |
| **Scenario 3. 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] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £108,006 | £106,460 |
| **Scenario 4. EAG base case + Stopping rule at ML 1 (HS 6)** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £100,000 | £100,000 |
| **Scenario 5. EAG base case + No discontinuation rule** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £125,674 | £126,618 |
| **Scenario 6. EAG base-case + Excluding background costs** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £100,000 | £100,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

**Abbreviations:** CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

### 4.3. EAG's exploratory analyses - starting and stopping rules

As noted in Section 3.2, the analyses presented by the company (addendum to the company response) exploring alternative starting and stopping rule criteria for cerliponase alfa were not performed at the cerliponase alfa list price or simple PAS price of [redacted]. Furthermore, these analyses did not incorporate the committee's preferences for the transition probabilities evidence source and excluded background care costs. The EAG presents in this section the results of exploratory analyses, which use hypothetical starting and stopping rules, while incorporating the committee's preference for the transition probabilities evidence source and including the background care costs. The EAG attempted to fulfil the committee's request by varying the stopping rule for subpopulations of individuals starting at different ML scores (ML 4, ML 5 and ML 6), and retaining the remaining EAG revised base case assumptions. The results of these exploratory analyses are presented in Table 7.

The EAG considers these analyses highly exploratory and not equivalent to subgroup analyses, as the underlying clinical effectiveness evidence is not specific to the subpopulations defined by the starting and stopping criteria in each analysis. Furthermore, the majority of the clinical evidence collected by the company did not reflect any particular set of starting and stopping criteria.

The exploratory analyses suggest that the estimates of cost effectiveness are sensitive to the choice of starting population and treatment stopping rule. In these analyses, starting treatment at higher ML scores results in more QALY gains but also increases the costs of treatment (the main component of the costs associated with cerliponase alfa) for individuals treated with cerliponase alfa. Across the different starting populations, the ICERs for cerliponase alfa vs. SoC reduce when treatment is discontinued at lower ML scores and for starting populations with ML score lower than 6, this does not impact the implied cost-effectiveness threshold when only patient utilities are considered. For patients starting treatment at ML score 6, the implied cost-effectiveness threshold is higher when treatment is allowed to continue throughout disease progression due to increased QALY gains for cerliponase alfa vs. SoC.

**Table 7 Exploratory analyses over the EAG's preferred assumptions (cerliponase alfa list price)**

| Scenario | | ICER (per QALY) | % change from base-case ICER | CE threshold* £/QALY | % change from base-case CE threshold |
|---|---|---|---|---|---|
| EAG revised base case | | [redacted] | [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% |
| 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% |
| 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% |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC and excluding carers and sibling utilities.
Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; ML, motor language.

## 5. Conclusions

The EAG considers that the analyses presented by the company do not reflect the committee stated preferences. The EAG base case analysis tried to incorporate the committee preferred assumption in regard to evidence source for the transition of probabilities (pooled 'all patient' dataset), which is one of the key cost-effectiveness drivers for cerliponase alfa. Since the committee did not state a preference for treatment discontinuation the EAG retained the assumption in their original base-case that cerliponase alfa would be stopped at ML score 1. The EAG further assumed the baseline distribution suggested by a clinical expert at the meeting as representative of current clinical practice, as the committee considered this plausible and did not state a preference for any particular baseline distribution. The EAG base case analysis suggests a deterministic ICER for cerliponase alfa vs. SoC of [redacted] per additional QALY. While this is a higher estimate than the company's corrected base case ([redacted] per additional QALY), both ICERs remain above the corresponding implied cost-effectiveness threshold (independent of whether only patient utilities or all utilities are included in the calculation of undiscounted incremental QALYs).

Using the EAG base-case analysis as a starting point to address the committee's request, the EAG scenario analyses suggest that the ICER for cerliponase alfa vs. SoC is more favourable for the technology when:

- Using pooled evidence from the company clinical programme (excluding MAA) to inform the transition probabilities (ICER of [redacted] per additional QALY). The company notes that there is no data from the clinical trial programme and from the MAA database that are not

affected by either the COVID-19 pandemic or the unavailability of cerliponase alfa at time of diagnosis for some patients.

- Using the baseline patient distribution suggested by clinical advice to the EAG as potentially reflective of clinical practice in 5 years' time according to clinical advice to the EAG, which was considered by the company the best estimate of a baseline distribution unaffected by COVID-19 (ICER of [redacted] per additional QALY).
- Excluding background care costs (ICER of [redacted] per additional QALY).

The analyses presented by the company and EAG to comply with the committee's request regarding the starting and stopping rules do not allow identify subgroups of individuals for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost-effective. This is because the underlying clinical effectiveness evidence is not specific to the subpopulations defined by the starting and stopping criteria in each individual analysis. The EAG exploratory analyses suggest that while it is more beneficial (i.e., yields higher incremental QALYs) to start treatment at higher ML scores and apply no stopping rule, the incremental costs of cerliponase alfa offset the benefits for all starting and stopping rules. While these analyses need to be interpreted cautiously, they provide some insight on the direction of impacts on cost-effectiveness across different sets of starting and stopping rules. They do not, however, fully characterise how much each subgroup might benefit from cerliponase alfa treatment compared to SoC. The EAG thinks that overall evidence available is not appropriate to guide the establishment of starting and stopping criteria.

## REFERENCES

1. Gissen P, Specchio N, Olaye A, Jain M, Butt T, Ghosh W, et al. Investigating health-related quality of life in rare diseases: A case study in utility value determination for patients with CLN2 disease (neuronal ceroid lipofuscinosis type 2). *Orphanet J Rare Dis* 2021;**16**:217.

## APPENDIX 1

### Table 8 Company's proposed base-case results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)

| Technologies | Total costs | Total LYG | Total QALYs | Incr. costs | Incr. LYG | Incr. QALYs | ICER (/QALY) | CE threshold* /QALY | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | All utilities | Excluding carer and sibling utilities |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £213,321 | NR |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |

**Abbreviations:** CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not recommended; QALYs, quality-adjusted life years; SoC, standard of care.

### Table 9 Company's corrected base-case results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)

| Technologies | Total costs | Total QALYs | Incr. costs | Incr. QALYs | ICER (/QALY) | CE threshold* /QALY | |
|---|---|---|---|---|---|---|---|
| | | | | | | All utilities | Excluding carer and sibling utilities |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £200,704 | £194,964 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |

**Abbreviations:** ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 10 Cost-effectiveness results of the EAG's base case and scenario analyses (cerliponase alfa PAS price)**

| Preferred assumption | Total Costs | Total QALYs | Incr. cost | Incr. QALYs | ICER £/QALY | CE threshold* £/QALY | |
|---|---|---|---|---|---|---|---|
| | | | | | | All utilities | Excluding carer and sibling utilities |
| **Company's corrected base case** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £200,704 | £194,964 |
| **EAG revised base-case** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £100,000 | £100,000 |
| **Scenario 1. EAG base-case + Baseline characteristics as clinical opinion of current practice in 5-year time (company's base-case)** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £139,528 | £137,428 |
| **Scenario 2. EAG base-case + Baseline characteristics as per EAG's original base-case (HS1 50%, HS2 50%)** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £142,584 | £140,405 |
| **Scenario 3. EAG base-case + Source of transition probabilities: Pooled data from Study 190-201/202 and Study 190-203, matched to Study 190-901** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £108,006 | £106,460 |
| **Scenario 4. EAG base case + Stopping rule at ML 1 (HS 6)** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £100,000 | £100,000 |
| **Scenario 5. EAG base case + No discontinuation rule** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £125,674 | £126,618 |
| **Scenario 6. EAG base-case + Excluding background costs** | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £100,000 | £100,000 |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC.

**Abbreviations:** CE, cost-effectiveness; HS, health state; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 11 Scenario analyses over the EAG's preferred assumptions (cerliponase PAS price)**

| Scenario | | ICER (per QALY) | % change from base-case ICER | CE threshold* £/QALY | % change from base-case CE threshold |
|---|---|---|---|---|---|
| EAG revised base case | | [redacted] | [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% |
| 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% |
| 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% |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC and excluding carers and sibling utilities.

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; ML, motor language.

# CONFIDENTIAL UNTIL PUBLISHED
# External Assessment Group Addendum to the Review of the Additional Evidence Submitted by the Company after ACM1

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]


| | |
|---|---|
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| **Date completed** | 03/09/2024 |

Following the first appraisal committee meeting (ACM1) on 12 June 2024, the committee requested, amongst other evidence, analyses that consider the inclusion of starting and stopping rules into the to identify subgroups of individuals for whom the evidence suggests cerliponase alfa is particularly clinically effective or cost-effective. In this addendum the Evidence Assessment Group (EAG) presents additional scenario analyses exploring alternative treatment stopping rules for a starting population with a motor language (ML) score of 6. These alternative stopping rules were varied over the EAG revised base case (see EAG review of the additional evidence submitted by the company), but using Study 190-203 (as per the company's proposed base case) as the evidence source to inform the transition probabilities.

The EAG highlights that these analyses were undertaken at NICE's request to explore the cost-effectiveness of a potential subgroup of patients diagnosed who start treatment at younger ages and with limited, or no, disease progression (ML score of 6). However, it is important to consider the uncertainties associated with the evidence collected in Study 190-203 (see Sections 3.9 and 4.2.7.1 of the EAG Evidence Assessment Report), particularly that affecting the long-term transition probabilities beyond the observed patient follow-up and the small sample size. The EAG reiterates that it is uncertain whether these patients might have a long period before disease progresses or have slower disease progression, and the use of Study 190-203 to inform transition probabilities may overestimate the health gains of cerliponase alfa compared to Standard of Care (SoC).

The results of the additional scenario analyses are presented at the company's list price for cerliponase alfa in Table 1. Results incorporating a patient access scheme (PAS) price corresponding to a [redacted] are shown in Table 2. [redacted]

**Table 1 Exploratory analyses over the EAG's preferred assumptions and using Study 190-203 to inform transition probabilities (cerliponase alfa list price)**

| Scenario | | ICER (per QALY) | % change from base-case ICER | CE threshold* £/QALY | % change from base-case CE threshold |
|---|---|---|---|---|---|
| EAG revised base case | | [redacted] | - | £100,000 | - |
| Starting ML | Treatment stop ML | | | | |
| 6 | No stopping | [redacted] | [redacted] | £300,000 | 200% |
| | 0 | [redacted] | [redacted] | £300,000 | 200% |
| | 1 | [redacted] | [redacted] | £299,987 | 200% |
| | 2 | [redacted] | [redacted] | £283,883 | 184% |
| | 3 | [redacted] | [redacted] | £265,402 | 165% |
| | 4 | [redacted] | [redacted] | £250,717 | 151% |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC and excluding carers and sibling utilities.

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; ML, motor language.

**Table 2 Scenario analyses over the EAG's preferred assumptions and using Study 190-203 to inform transition probabilities (cerliponase PAS price)**

| Scenario | | ICER (per QALY) | % change from base-case ICER | CE threshold* £/QALY | % change from base-case CE threshold |
|---|---|---|---|---|---|
| EAG revised base case | | [redacted] | - | £100,000 | - |
| Starting ML | Treatment stop ML | | | | |
| 6 | No stopping | [redacted] | [redacted] | £300,000 | 200% |
| | 0 | [redacted] | [redacted] | £300,000 | 200% |
| | 1 | [redacted] | [redacted] | £299,987 | 200% |
| | 2 | [redacted] | [redacted] | £283,883 | 184% |
| | 3 | [redacted] | [redacted] | £265,402 | 165% |
| | 4 | [redacted] | [redacted] | £250,717 | 151% |

*Applicable cost-effectiveness threshold given undiscounted QALY gains for cerliponase alfa vs. SoC and excluding carers and sibling utilities.

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; ML, motor language.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Highly specialised technology evaluation

# Cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) [ID6145]

# Additional analyses

**August 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6145_CerliponaseAlfa_CLN2_additional_analyses v3.0_[Redacted].docx | 3.0 | No – Redacted | 29th August 2024 |


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# List of abbreviations

| Abbreviation | Description |
|---|---|
| ACM | Appraisal committee meeting |
| CLN2 | Ceroid lipofuscinosis type 2 |
| EAG | External Assessment group |
| EAP | Expanded access programme |
| ECG | Electrocardiogram |
| FAC | Factual accuracy check |
| HST | Highly specialised technology |
| HSUV | Health state utility value |
| ICER | Incremental cost-effectiveness ratio |
| LYG | Life years gained |
| MAA | Managed access agreement |
| ML | Motor language |
| NICE | National Institute for Health and Care Excellence |
| PAS | Patient access scheme |
| QALY | Quality-adjusted life year |
| SmPC | Summary of product characteristics |
| SoC | Standard of care |


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# 1 Context

In 2019, NICE recommended cerliponase alfa for the treatment of patients with ceroid lipofuscinosis type 2 (CLN2), within the context of a managed access agreement (MAA; HST12) (1). Following the company's resubmission on 31st January 2024, and the subsequent committee meeting held on 12th June 2024, the NICE committee requested further company analyses to aid decision-making. The company considers that two of the assumptions in the committee base case are not reflective of clinical practice and therefore propose an alternative base case.

Results of the committee and the alternative company proposed base cases are presented using the discounted price for cerliponase alfa, including:

[redacted]

Results assuming either the list price or the [redacted] are presented in Appendix A.

For each analysis, incremental cost-effectiveness ratios (ICER) are presented alongside the effective HST cost-effectiveness threshold. It should be noted that it is not possible to capture the following within the cost-effectiveness estimates:

- 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 of an affected child.


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# 2 Assumptions

A summary of the assumptions for the EAG, committee, and company proposed base cases are presented in Table 3.

As noted by the committee, current NICE guidance states that, 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, a non-reference case analysis may be considered with background care costs removed (2).

CLN2 disease is associated with a high cost of care, even in the absence of active treatment. The annual cost of each type of background care is presented in Table 1.

**Table 1: Annual cost of background care**

| Type of background care | Annual cost |
|---|---|
| Health state (health and social care visits) | £5,269 to £33,539 (dependent on health state) |
| Vision loss | £4,561 |
| Psychiatric and behavioural support | £1,316 |
| Residential care | £49,359 |

Treatment with cerliponase alfa is associated with longer-term survival compared with SoC, resulting in increased background care costs that do not represent direct, intrinsic consequences of treatment.

The following background care costs were therefore excluded from the committee and company proposed base cases:

- Health state costs
- Vision loss costs
- Psychiatric and behavioural support costs
- Residential care costs.

An additional set of results is also presented for the committee base case in which background care costs are included.

The committee requested analyses for the health state distribution at model entry using data taken from current clinical practice that excludes patients where diagnosis or treatment initiation was delayed because of COVID-19. However, this analysis is not possible due to the following:


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- Data for age at CLN2 diagnosis from the clinical trial programme and from the MAA are incomplete
- It is anticipated that the effect of the COVID-19 pandemic is still a factor that may be affecting diagnosis, with some children potentially yet to be diagnosed as a direct impact of pandemic-related clinical delays (company submission Document B, Section B.2.12.2)
- Although data are available from prior to the COVID-19 pandemic, time to treatment initiation was primarily determined by when cerliponase alfa became available.
- Available data could not account for delays in CLN2 diagnosis.

There are therefore no data from the clinical trial programme and from the MAA database that are not affected by either the COVID-19 pandemic or the unavailability of cerliponase alfa at time of diagnosis for some patients. The clinician estimate of the baseline distribution in 5 years' time was therefore used in the committee base case as the best estimate of a baseline distribution unaffected by COVID-19.

The committee requested analyses considering the inclusion of starting and stopping rules for cerliponase alfa. As of July 2024, no patients have discontinued treatment with cerliponase alfa as a result of reaching the stopping criteria in the MAA. Furthermore, the clinical trial programmes for cerliponase alfa do not provide evidence for the implementation of starting and/or stopping criteria. As such, no clinical evidence exists for its implementation.

To establish starting/stopping criteria which may be used in clinical practice, the company sought insights from clinical experts and representatives of the patient advocacy group. Clinical expert opinion highlighted that given the rarity and heterogeneity of CLN2, criteria for treatment discontinuation would currently be determined on a case-by-case basis and may be dependent on numerous factors including ML score, patient-reported outcomes (PROs), and the intensity of the patient's progressive symptoms. Experts were unanimous that ML score alone is not an appropriate measure for determining treatment discontinuation. However, in clinical practice, it is expected that on average patients may discontinue treatment at an ML score of either 1 or 0, therefore a stopping rule at ML 1 was considered in the base case and ML 0 was considered as a scenario analysis.

The company has committed to consolidating and sharing additional information for consideration, once all starting and stopping criteria discussions with clinicians and patient advocacy representatives have been held.


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It is important to note that in the economic model, the ICER and threshold change in a relatively linear way in response to changes in discontinuation rates or stopping rules. Table 2 presents the results of the committee base case assuming stopping criteria at an ML score of 0 and 1 and the respective thresholds. Assuming a stopping criteria of ML 0 results in a 19% increase in the ICER, but also a 21% increase in the cost-effectiveness threshold, and so the cost-effectiveness conclusions remain unchanged. Therefore, the company does not consider stopping criteria to be a key driver of cost-effectiveness.

**Table 2: Discontinuation ICER and threshold results (with discounted price for cerliponase alfa)**

| | ICER (cost/QALY) | Threshold |
|---|---|---|
| Stopping criteria at ML 1 | [redacted] | £139,273 |
| Stopping criteria at ML 0 | [redacted] | £167,900 |
| Ratio | 1.19 | 1.21 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year.

The company base case makes two amendments to the committee base case:

- Transition probabilities are taken from Study 190-203 only:
    - As data from Study 190-201/202 encompass treatment pauses between the end of the EAP and the start of the MAA and therefore reflects transitions for more progressed patients who did not have cerliponase alfa available at the time of diagnosis.
    - Additionally, at the beginning of Study 190-201, 6 patients were enrolled in the study dose-escalation phase under the inclusion criteria of an ML score between 3 and 6 inclusive. During the escalation phase three patients experienced disease progression to ML scores of 2 and 1; these patients remained in the study as eligibility was determined according to the screening assessment ML score, and therefore these patients remained eligible for study inclusion.
- ECGs are not applied for cardiac-normal patients, in line with clinical expert advice that this would not be undertaken in clinical practice; note that an annual cardiologist appointment is applied for all patients.


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**Table 3: Base case assumptions**

| | Base case | | |
|---|---|---|---|
| | **EAG** | **Committee** | **Company proposal** |
| Baseline distribution | Aligned with HST12<br>• Health state 1: 50%<br>• Health state 2: 50% | Current clinical practice excluding patients where diagnosis or treatment initiation was delayed due to COVID-19†<br>• Health state 1: 50%<br>• Health state 2: 35%<br>• Health state 3: 13%<br>• Health state 4: 3% | |
| | | Scenario considering baseline distribution derived from clinical expert opinion‡<br>• Health state 1: 28.5%<br>• Health state 2: 28.5%<br>• Health state 3: 43.0% | - |
| Source of transition probabilities | All patients' dataset | Pooled data from Study 190-201/202 and Study 190-203 | Study 190-203 |
| Initial stabilisation | • 80% of ML 6 are initial stabilisers<br>• Stabilise for 6 years<br>• After 6 years, transition at 50% of the rate of other patients | | |
| Progressive symptoms | Assumptions aligned with the company submission (Document B, Section B.3.3.3) | | |
| Method to estimate transition probabilities | Assumptions aligned with the company submission (Document B, Section B.3.3.2) | | |
| Backward transitions to healthier health states | Permitted | | |
| Vision loss | Cerliponase alfa has no impact on vision loss | | |
| Source of HSUVs | Gissen et al. 2021 | | |


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| | Base case | | |
|---|---|---|---|
| | **EAG** | **Committee** | **Company proposal** |
| ECG monitoring costs | Included:<br>• ECG every 6 months for all patients<br>• ECG at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>• One annual cardiologist appointment for all patients | | Included:<br>• ECG included at every infusion for a proportion of patients with a history of bradycardia, conduction disorder<br>• One annual cardiologist appointment for all patients |
| Neurodisability mortality | Included in all health states | | |
| Background care costs¶ | Included | Excluded<br>• Second set of results presented with background care costs included | Excluded |
| Starting and stopping criteria§ | • No starting rule<br>• Stopping rule at ML 0 | • No starting rule<br>• Stopping rule at ML 1<br><br>Scenario considering stopping rule at ML 0 | • No starting rule<br>• Stopping rule at ML 1 |

†Baseline distribution derived from clinical opinion of the distribution in 5-years' time was considered as a reasonable proxy; ‡Assuming a starting age of 3.5 years, aligned with the baseline age in the original HST12 and clinical opinion of the baseline distribution in 5-years' time; ¶Background care costs include health state costs, vision loss costs, psychiatric and behavioural support costs, and residential care costs; §In order to consider alternative starting rules in the economic model, selected starting distributions are reweighted to consider proportion in associated ML scores only.
Abbreviations: EAG, external assessment group; ECG, electrocardiogram; HSUVs, health state utility values; ML, motor language.


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# 3 Results

All results in this section use the discounted price for cerliponase alfa, considering the following discounts:

[redacted]

## 3.1 Results - committee base case

The derivation of the committee's base case (excluding background care costs) from the EAG base case at cerliponase alfa discounted price is presented in Table 4.

Additionally, the company noted and subsequently amended inconsistencies in the EAG's model; details of the amendments made are presented in Appendix B.

**Table 4: Derivation of the committee base case – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| | | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|
| 1 | EAG base case | [redacted] | [redacted] | [redacted] | £169,561† |
| 2 | 1 + vision loss correction + discontinuation correction | [redacted] | [redacted] | [redacted] | £157,941 |
| 3 | 2 + baseline distribution from clinical opinion in 5-years' time | [redacted] | [redacted] | [redacted] | £154,943 |
| 4 | 3 + transition probabilities from pooled Study 190-201/202 & 203 | [redacted] | [redacted] | [redacted] | £167,900 |
| 5 | 4 + cerliponase alfa treatment discontinuation at ML score 1 | [redacted] | [redacted] | [redacted] | £139,273 |
| 6 | 5 + background care costs removed | [redacted] | [redacted] | [redacted] | £139,273 |
| 7 | Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |

†Note, the EAG base case threshold is incorrectly reported in the following documentations: ACM slides and EAG report Table 1.
Abbreviations: ACM, Appraisal committee meeting; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year; SoC, standard of care.


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Results of the committee base case (excluding background care costs) and scenarios are presented in Table 5 and Table 6, respectively.

**Table 5: Base-case results – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care.

**Table 6: Scenario results – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Scenario | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|
| Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| Baseline distribution derived from committee clinical expert opinion | [redacted] | [redacted] | [redacted] | £100,000 |
| Treatment discontinuation at ML 0 | [redacted] | [redacted] | [redacted] | £167,900 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year; SoC, standard of care.

Results of the committee base case (including background care costs) are presented in Table 7.

**Table 7: Base-case results (including background care costs) – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care.


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## 3.2 Results – company base case proposal

The derivation of the company base case from the committee's base case is presented in Table 8, and the results of the company proposed base case considering the discounted price for cerliponase alfa are presented in Table 9.

**Table 8: Derivation of the company proposed base case – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| | | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|
| 1 | Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| 2 | 1 + transition probabilities derived from Study 190-203 | [redacted] | [redacted] | [redacted] | £213,321 |
| 3 | 2 + ECG monitoring at every infusion for cardiac abnormal patients only | [redacted] | [redacted] | [redacted] | £213,321 |
| 4 | Company base case proposal | [redacted] | [redacted] | [redacted] | £213,321 |

Abbreviations: ECG, electrocardiogram; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

**Table 9: Base-case results – cerliponase alfa vs SoC (with discounted price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER vs baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £213,321 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.


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# 4 References

1. National Institute for Health and Care Excellence (NICE). Final evaluation document. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. 2019.

2. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (last accessed October 2023). 2022.


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# Appendix A – Results at alternative prices

## PAS price results

Results of the committee base case considering the [redacted] for cerliponase alfa are presented in Table 10, Table 11 and Table 12, with the company base case proposal presented in Table 13.

### *Committee base case*

**Table 10: Base-case results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 11: Scenario results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Scenario | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|
| Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| Baseline distribution derived from committee clinical expert opinion | [redacted] | [redacted] | [redacted] | £100,000 |
| Treatment discontinuation at ML 0 | [redacted] | [redacted] | [redacted] | £167,900 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care.


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**Table 12: Base-case results (including background care costs) – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; SoC, standard of care

### *Company base case*

**Table 13: Base-case results – cerliponase alfa vs SoC (with PAS price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £213,321 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; SoC, standard of care.

## List price results

Results of the committee base case considering the list price for cerliponase alfa are presented in Table 14, Table 15 and Table 16, with the company base case proposal presented in Table 17.


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### *Committee base case*

**Table 14: Base-case results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.

**Table 15: Scenario results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Scenario | Incremental costs (£) | Incremental QALYs | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|
| Committee base case | [redacted] | [redacted] | [redacted] | £139,273 |
| Baseline distribution derived from committee clinical expert opinion | [redacted] | [redacted] | [redacted] | £100,000 |
| Treatment discontinuation at ML 0 | [redacted] | [redacted] | [redacted] | £167,900 |

Abbreviations: ICER, incremental cost-effectiveness ratio; ML, motor language; QALY, quality-adjusted life year; SoC, standard of care.

**Table 16: Base-case results (including background care costs) – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £139,273 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.


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### *Company base case*

**Table 17: Base-case results – cerliponase alfa vs SoC (with list price for cerliponase alfa)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) | Threshold |
|---|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - | £213,321 |
| Cerliponase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care.


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# Appendix B – Additional company corrections

## Vision loss approach

During the EAG factual accuracy check (FAC), the company noted that the EAG's calculation of the proportion of patients with vision loss in the model resulted in incorrect estimates of the vision loss utility multiplier. Despite this being raised by the company during the FAC, the EAG indicated that this was not an error, and highlighted that their approach was in line with HST12. Nevertheless, the company believes that this error remains, resulting in incorrect estimates for the vision loss utility multiplier.

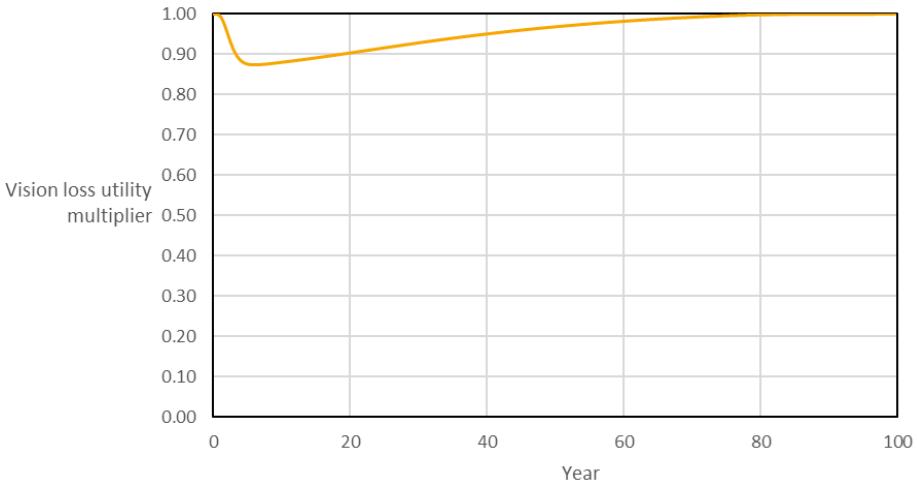
For the calculation of QALYs, the proportion of patients with vision loss is used to determine the vision loss utility multiplier, which is applied to QALY calculations of all alive patients. The approach taken by the EAG, aligned with HST12, calculates the proportion with vision loss as an absolute proportion of all modelled patients and therefore, the proportion with vision loss increases then decreases to 0% as patients enter the absorbing death state. As a result, the vision loss utility multiplier decreases initially, then increases to one as patients enter death, the absorbing state.

The proposed approach by the company is to calculate the proportion with vision loss to align with the QALY and cost calculations as follows:

- QALYs: the proportion of patients with vision loss out of all patients alive
- Costs: the total proportion of patients with vision loss

The corrected and uncorrected approaches to modelling vision loss are presented in Figure 1 and Figure 2 respectively. The corrected approach shows the multiplier reaching 0.87 once all patients experience vision loss or reach age 20 over the course of the model horizon.

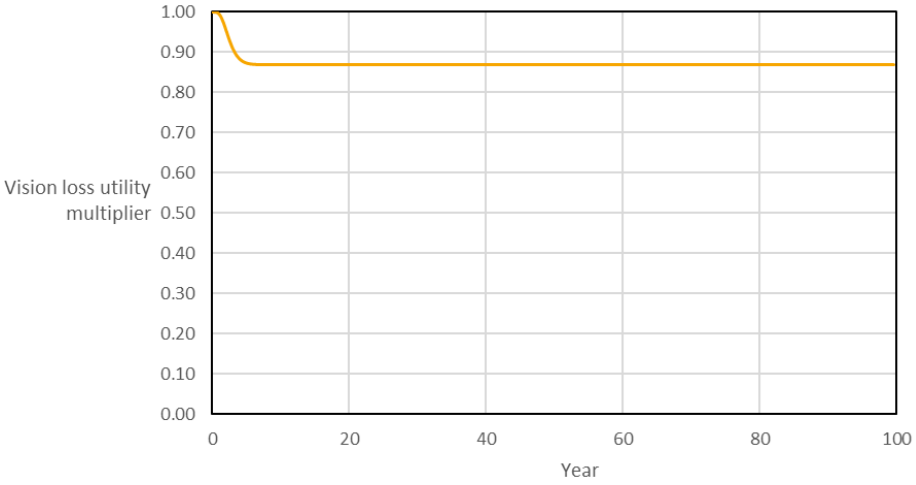
**Figure 1: Vision loss utility multiplier – HST12 approach**





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**Figure 2: Vision loss utility multiplier – Company correction**




Results presented in Section 3 adjust for the impact of correcting this assumption.

## Discontinuation transition approach

In the company's submission, once patients discontinue treatment with cerliponase alfa, they are assumed to switch to transition probabilities for standard of care (SoC). However, the EAG noted that the approach to modelling treatment discontinuation was inconsistent, remarking that once patients discontinue treatment 'some treatment effect of cerliponase alfa remains. The company has provided a correction to this assumption, in which patients receiving treatment with cerliponase alfa switch to transition probabilities for SoC, at the point of entering the health state associated with the discontinuing motor language (ML) score. Results presented in Section 3 adjust for the impact of correcting this approach.


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# CONFIDENTIAL UNTIL PUBLISHED
# External Assessment Group Additional Analysis after ACM3

# Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12) [ID6145]


| | |
|---|---|
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| **Date completed** | 11/04/2025 |

The External Assessment Group (EAG) was requested by NICE to present the cost-effectiveness results for the NICE committee's preferred assumption for the incident population, as decided at the third appraisal committee meeting (ACM3). Table 1 summarises the NICE committee's preferred assumptions for the incident population, alongside those of the company for this population; corresponding cost-effectiveness results are presented in Table 2.

**Table 1 Preferred assumptions for the incident population**

| Assumption | NICE committee |
|---|---|
| BL distribution* | Realistic scenario in the company's advisory board (December 2004) |
| HS1 (ML 6) | [redacted] |
| HS2 (ML 5) | [redacted] |
| HS3 (ML 4) | [redacted] |
| HS4 (ML3) | [redacted] |
| Source of transition probabilities | Pooled 'all patients' dataset (matched to Study 190-901) |
| Initial stabilisation with cerliponase alfa | |
| Proportion of stabilisers | 80% at HS1(ML6) at BL |
| Risk reduction for initial stabilisers ** | 50% |

*the starting age assumed for the incident population is 2.625 years; ** beyond 6 years, compared to non-stabilisers
**Abbreviations:** EAG, external assessment group; HS, health state; ML, motor language.

**Table 2 Additional cost-effectiveness results– Committee's preference for the incident population at ACM3**

| Technologies | Total costs | Total QALYs | Incr. costs | Incr. QALYs* | ICER (/QALY) | CE threshold | | LY in HS1 |
|---|---|---|---|---|---|---|---|---|
| | | | | | | including all utilities | Including only patient utilities | |
| SoC | [redacted] | -0.63 | | | | | | 0.35 |
| Cerliponase alfa | [redacted] | 9.03 | [redacted] | 9.65 | [redacted] | [redacted] | [redacted] | 12.66 |